Bohn, Brent

From: Lee, Janice
Sent: Tuesday, April 01, 2014 5:10 PM
To: Sams, Reeder; Cowden, John
Cc: Chiu, Weihsueh
Subject: RE: Arsenic: Proposed Approach for Meta-Analyses

Categories: Record Saved - Private

Sure, I can do that. I'll talk to Amanda and Krista.
Would a 1 or 2 week turnaround seem reasonable? It's 8 pages, not too long.

Janice

From: Sams, Reeder
Sent: Tuesday, April 01, 2014 2:11 PM
To: Lee, Janice; Cowden, John
Cc: Chiu, Weihsueh
Subject: RE: Arsenic: Proposed Approach for Meta-Analyses

Janice,

Sounds good to me. Would you please coordinate the review?

Thanks,
Reeder

Reeder L. Sams II, Ph.D.
Deputy Director (Acting), RTP Division
NCEA/ORD/USEPA
RTP, NC 27711

Phone: 919-541-0661
Fax: 919-541-0245

From: Lee, Janice
Sent: Tuesday, April 01, 2014 10:17 AM
To: Sams, Reeder; Cowden, John
Subject: FW: Arsenic: Proposed Approach for Meta-Analyses

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What are your thoughts? Should people who did it for TCE take a look?

Janice

From: Chiu, Weihsueh
Sent: Monday, March 31, 2014 5:14 PM
To: Lee, Janice
Subject: RE: Arsenic: Proposed Approach for Meta-Analyses

Hi Janice,

I'd be happy to take a look, but I'm not sure I'm the best person to review this. In fact, I'd suggest that the epidemiology WG should be consulted. Jennifer Jinot and Cheryl Scott did the meta-analysis for cancer and TCE, and with Glinda Cooper also did in a meta-analysis for schleroderma and TCE.

Regards,
Weihsueh

Weihsueh Chiu, PhD
Chief, Toxicity Pathways Branch
IRIS Division, National Center for Environmental Assessment
U.S. Environmental Protection Agency - 8601P
Washington, DC 20460
(703) 347-8607 (voice)
(703) 347-8699 (fax)
chiu.weihsueh@epa.gov

From: Lee, Janice
Sent: Monday, March 31, 2014 3:33 PM
To: Chiu, Weihsueh
Subject: FW: Arsenic: Proposed Approach for Meta-Analyses

Hi Weihsueh,

Attached is the proposed approach for hazard ID meta-analyses for arsenic. Since you did meta-analysis for TCE, it'd be great if you can take a look.

Thanks!
Janice

From: Cowden, John
Sent: Monday, March 31, 2014 2:53 PM
To: Davis, Allen; Gift, Jeff; Luben, Tom; Kirrane, Ellen
Cc: Lee, Janice; Sams, Reeder
Subject: FW: Arsenic: Proposed Approach for Meta-Analyses

Hi Ellen, Allen, Jeff, and Tom,

Happy Monday! I hope that things are going well for you today.

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Let me know if you have any questions. Have a great afternoon!

John

John Cowden, Ph.D.
Hazardous Pollutant Assessment Group (HPAG)
National Center for Environmental Assessment (NCEA)

U.S. Environmental Protection Agency - RTP
(919) 541-3667

From: Turley, Audrey [mailto:Audrey.Turley@icfi.com]
Sent: Friday, March 28, 2014 6:23 PM
To: Cowden, John; Lee, Janice; Sams, Reeder
Cc: Eftim, Sorina; Mendez Jr, William; Burch, Dave
Subject: Arsenic: Proposed Approach for Meta-Analyses

John, Janice, and Reeder,

The attached memo describes our proposed approach for meta-analyses for hazard identification. We look forward to discussing it with you on either Thursday or Friday of next week.

Are you available at any of these times?
Thursday, April 3
- 11-12
- 2:30-3:30

Friday, April 4
- 11-12
- 2-3
- 3-4

Thank you,
Audrey

AUDREY TURLEY | Senior Manager | 919.293.1621 (o) | 919.599.3601 (m) | audrey.turley@icfi.com | icfi.com
ICF INTERNATIONAL | 2635 Meridian Parkway, Suite 200, Durham, NC 27713

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ICF INTERNATIONAL | 2635 Meridian Parkway, Suite 200, Durham, NC 27713

Bohn, Brent 1061

From: Powers, Christina
Sent: Monday, June 30, 2014 2:22 PM
To: Sams, Reeder
Cc: Powers, Christina
Subject: RE: Thank You

Thanks for your warm note and support throughout this work Reeder.

Have we developed a thank you note to send to stakeholders who attended in person or via webinar for their time and contributions? You likely already have a plan in place, but I wanted to check just in case since I think it could help continue the positive momentum of the meeting.

As always, don't hesitate to contact me if I can be of assistance with this potential action item, or others.

Best,
Christy

From: Sams, Reeder
Sent: Monday, June 30, 2014 2:08 PM
To: Luben, Tom; Kirrane, Ellen; Lee, Janice; Cowden, John; Thomas, David; Andrew Rooney; Powers, Christina; Gift, Jeff; Jones, Ryan
Subject: Thank You

Arsenic Dream Team,

I wanted to take a moment and thank each and every one of you. In my view the arsenic meeting held last week was a big success. It takes a significant effort on behalf of the individuals and the team, in addition to the effort to travel. Everyone did a great job contributing to and leading useful discussions with the stakeholders.

Congratulations and Thank you,

Best Regards,
Reeder

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RTP, NC 27711

Phone: 919-541-0661
Fax: 919-541-0245

Bohn, Brent 1062

From: Sams, Reeder
Sent: Monday, June 30, 2014 2:08 PM
To: Luben, Tom; Kirrane, Ellen; Lee, Janice; Cowden, John; Thomas, David; Andrew Rooney; Powers, Christina; Gift, Jeff; Jones, Ryan
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Phone: 919-541-0661
Fax: 919-541-0245

Bohn, Brent 1066

From: Lee, Janice
Sent: Monday, June 30, 2014 9:44 AM
To: Powers, Christina; Luben, Tom; Kirrane, Ellen; Thomas, David
Subject: FW: How politics derailed EPA science on arsenic, endangering public health (Center for Public Integrity Article)

In case you didn't see this story. It's an interesting read.

From: Shams, Dahnish
Sent: Saturday, June 28, 2014 9:51 AM
To: Vandenberg, John; Walsh, Debra; Flowers, Lynn; Cogliano, Vincent; Jones, Samantha; Perovich, Gina; Sams, Reeder; Cowden, John; Lee, Janice; Berner, Ted; Birchfield, Norman; Bussard, David; Ross, Mary; Jarabek, Annie
Cc: Deener, Kathleen; D'Amico, Louis
Subject: How politics derailed EPA science on arsenic, endangering public health (Center for Public Integrity Article)

http://www.publicintegrity.org/2014/06/28/15000/how-politics-derailed-epa-science-arsenic-endangering-p

How politics derailed EPA science on arsenic, endangering public health

Delay keeps pesticides with arsenic on the market

By David Heath email

6 hours, 33 minutes ago Updated: 2 hours, 22 minutes ago

Wendy Brennan and her granddaughter, Madelyn Begin, in the kitchen of Brennan's home in Mount Vernon, Maine. Brennan had a filter installed on her tap after she learned her drinking water contained arsenic. Amy Temple

MOUNT VERNON, Maine — Living in the lush, wooded countryside with fresh New England air, Wendy Brennan never imagined her family might be consuming poison every day.

But when she signed up for a research study offering a free T-shirt and a water-quality test, she was stunned to discover that her private well contained arsenic.

"My eldest daughter said ... 'You're feeding us rat poison.' I said, 'Not really,' but I guess essentially ... that is what you're doing. You're poisoning your kids," Brennan lamented in her thick Maine accent. "I felt bad for not knowing it."

Brennan is not alone. Urine samples collected by the Centers for Disease Control and Prevention from volunteers reveal that most Americans regularly consume small amounts of arsenic. It's not just in water; it's also in some of the foods we eat and beverages we drink, such as rice, fruit juice, beer and wine.

Under orders from a Republican-controlled Congress, the Environmental Protection Agency in 2001 established a new drinking-water standard to try to limit people's exposure to arsenic. But a growing body of research since then has raised questions about whether the standard is adequate.

The EPA has been prepared to say since 2008, based on its review of independent science, that arsenic is 17 times more potent as a carcinogen than the agency now reports. Women are especially vulnerable. Agency scientists calculated that if 100,000 women consumed the legal limit of arsenic every day, 730 of them would eventually get bladder or lung cancer from it.

After years of research and delays, the EPA was on the verge of making its findings official by 2012. Once the science was complete, the agency could review the drinking water standard.

But an investigation by the Center for Public Integrity found that one member of Congress effectively blocked the release of the EPA findings and any new regulations for years.

Arsenic levels in groundwater across the U.S.

By Jared Bennett and Chris Zubak-Skees

6 hours, 33 minutes ago

Arsenic makes up part of the Earth's crust and is commonly found in groundwater. In 2001, the Environmental Protection Agency lowered the drinking-water standard from 50 parts per billion of arsenic to 10 parts per billion. The agency had initially proposed a limit of five parts per billion but faced criticism that it would be too costly for water companies to hit that target.
Arsenic is known to cause a variety of cancers as well as being linked to heart disease, strokes and diabetes. Recent research has found an association between arsenic below 10 parts per billion and IQ deficits in children.
This map is based on arsenic readings from 45,000 wells collected by the United States Geological Survey throughout the country going back four decades. In addition, the states of Texas and Minnesota provided data gathered on arsenic in private wells. In several other states, few readings were available.

> "I jokingly say that arsenic makes lead look like a vitamin ... the arsenic effects ... impact everything that's going on, every organ system."

- Joseph Graziano, professor at Columbia University who led Maine research

Listen to the story on the national public radio show, 'Reveal'

What to do if your drinking water contains arsenic

By David Heath

6 hours, 33 minutes ago

It is a battle between politics and science. Mining companies and rice producers, which could be hurt by the EPA's findings, lobbied against them. But some of the most aggressive lobbying came from two pesticide companies that sell a weed killer containing arsenic.

The EPA had reached an agreement with those companies to ban most uses of their herbicide by the end of last year. But the agreement was conditioned on the EPA's completing its scientific review. The delay by Congress caused the EPA to suspend its ban. The weed killer, called MSMA, remains on the market.

Turning to a powerful lawmaker for help is one tactic in an arsenal used by industry to virtually paralyze EPA scientists who evaluate toxic chemicals. In 2009, President Obama signed an executive memorandum to try to stop political interference with science. That same year, the EPA unveiled an ambitious plan to evaluate far more chemicals each year than had been done in either the Bush or Clinton administrations.

But in 2012 and 2013, the EPA has managed to complete only six scientific evaluations of toxic chemicals, creating a backlog of 47 ongoing assessments. It's a track record no better than past administrations. The Center found that a key reason for this is the intervention by a single member of Congress.

The story of arsenic shows how easily industry thwarted the Obama's administration's effort to prevent interference with science.

Wendy Brennan's granddaughter, Abigail Begin, near the family's water well.
Amy Temple

Lifetime cancer risk

How many people out of 100,000 would eventually get cancer if they consumed the EPA drinking water limit every day for these carcinogens?

A ubiquitous poison

Arsenic is virtually synonymous with poison. But it's also everywhere, found naturally in the Earth's crust. Even if the toxin were eliminated from drinking water, people would still consume it in food, a more vexing problem to address.

Scientists are debating whether there is such a thing as a safe level of arsenic. New research has raised questions whether even low levels of arsenic can be harmful, especially to children and fetuses.

The findings of the study Wendy Brennan enrolled in were published in April. Researchers from Columbia University gave IQ tests to about 270 grade-school children in Maine. They also checked to see if there was arsenic in their tap water at home. Maine is known as a hot spot for arsenic in groundwater.

The researchers found that children who drank water with arsenic — even at levels below the current EPA drinking water standard — had an average IQ deficit of six points compared to children who drank water with virtually no arsenic.

The findings are eerily similar to studies of lead, a toxin considered so dangerous to children that it was removed from paint and gasoline decades ago. Other studies have linked arsenic to a wide variety of other ailments, including cancer, heart disease, strokes and diabetes.

"I jokingly say that arsenic makes lead look like a vitamin," said Joseph Graziano, a Columbia professor who headed the Maine research. "Because the lead effects are limited to just a couple of organ systems — brain, blood, kidney. The arsenic effects just sweep across the body and impact everything that's going on, every organ system."

For 15 years, Brennan and her family drank water with arsenic levels five times greater than the current drinking-water standard. She has no way of knowing what effect this has had on her two daughters.

Carrington Brennan, now 14, says it bothers her to think that drinking water may have affected her intelligence.
"It shocked and scared me, I guess," she said. "I think it should be prevented in future cases."

Wendy Brennan, center, outside her home with husband Peter, daughter Caitlyn and granddaughter Madelyn Begin.
Amy Temple

Chemical reviews lag

It's the job of the EPA to protect the public from toxic chemicals. To do that, the agency must first review the scientific literature to determine which chemicals are harmful and at what doses. This duty falls on an obscure program with a drab bureaucratic name, the Integrated Risk Information System (IRIS).

There are tens of thousands of chemicals on the market and by one estimate, 700 new chemicals are introduced every year. Yet since 1987, IRIS has completed evaluations on only 557 of them.

The last time IRIS analyzed arsenic was in 1988, just a year before the Safe Drinking Water Act called for the EPA to set a new drinking-water standard for the toxin. The EPA missed that deadline, so in 1996, a Republican-controlled Congress gave the agency five more years to comply. The EPA turned to the prestigious National Academy of Sciences for help. Scientists there reviewed the EPA's 1988 analysis. They said it was badly out of date and underestimated the risk of arsenic.

After the EPA set a new drinking-water standard in 2001, the IRIS program moved to update its analysis of arsenic. EPA scientists spent five years reviewing hundred of studies before sending a draft report to the White House's Office of Management and Budget in October 2008.

EPA scientists concluded that arsenic was 17 times more potent as a carcinogen than the agency currently reports. Put another way, the risk of someone eventually getting cancer from drinking the legal limit of arsenic every day is 60 times greater than any other toxin regulated by drinking-water laws.

Total scientific assessments by the EPA

During the Clinton and Bush administrations, scientific assessments of toxic chemicals hit a logjam. The EPA promised to break the logjam but has not succeeded.

The White House at that point had become a nemesis of EPA scientists, requiring them to clear their science through OMB starting in 2004. Scientific assessments were often sent to OMB only to die, seemingly the victim of political influence. A stinging report by the Government Accountability Office in 2008 said that IRIS was at serious risk of becoming obsolete, unable to keep up with the workload or the science. The GAO noted that in 2007 the EPA sent 16 assessments to OMB, where they got held up. That year, the agency managed to complete only two assessments.

Within five months of Obama taking office, the EPA wrested back control of the process. The agency also set up an ambitious timetable to complete toxic-chemical assessments within two years. By that point, the arsenic assessment had already been in the works for six.

The arsenic draft had to go through an external peer-review before being considered valid. But IRIS officials were optimistic about completing it by the end of 2011.

Meanwhile, in an entirely different office within the EPA, negotiations were under way that would ultimately prevent IRIS from finishing its work.

Arsenic: decades of delays

Groundwater fears

Veterans Community Park is one of the busiest parks in Naples, Florida, with softball fields, basketball and tennis courts and a playground. In early 2004, Collier County began spraying the herbicide MSMA on the fields to control weeds. But soon, tests detected high levels of arsenic in the groundwater.

It wasn't the first time alarms had sounded about MSMA. Tests at nine golf courses using the weed killer had detected significant levels of arsenic in shallow groundwater and ponds, a concern because 90 percent of all drinking water in Florida comes from wells. The EPA had already banned all pesticides containing inorganic arsenic, considered to be the most toxic form of the metal. But evidence showed that the organic arsenic in MSMA converts to inorganic in soil. EPA scientists feared that MSMA could be contaminating drinking water.

In 2006, the EPA's Office of Prevention, Pesticides and Toxic Substances announced plans to ban all uses of herbicides containing arsenic and began negotiating with the few companies still selling them. Within three years, they had reached an agreement. The pesticide companies would phase out all uses of MSMA, except on cotton fields, by the end of 2013.

But the agreement included a condition. It required the EPA to complete a scientific review of arsenic before the ban could take effect. The pesticide office apparently assumed that the IRIS assessment, then six years in the making, would be done by then.

In all likelihood, IRIS would have met the deadline. But two pesticide companies and their lobbyist turned to Congress.

The two companies are Drexel Chemical Co. of Memphis, Tennessee, and Luxembourg-Pamol, whose parent, Luxembourg Industries, is based in Tel Aviv, Israel. Both are family-owned. Luxembourg-Pamol doesn't release sales figures; Drexel Chemical says its sales exceed $100 million a year.

Though anyone can buy MSMA, the label cautions that it should be sprayed only on cotton fields, sod farms, highway shoulders and golf courses. The market for MSMA is likely worth several million dollars for these companies. The EPA estimated in 2006 that about 3 million pounds of MSMA and another similar compound were sold each year in the United States. The weed killer retails for about $5 a pound.

An example of the herbicide MSMA for sale on Amazon.com

The companies joined forces to hire Charlie Grizzle, a lobbyist who worked as an EPA assistant administrator during the President George H. W. Bush era. When the EPA released a public draft of its arsenic assessment in February 2010, the pesticide companies countered with a unique argument.

Michal Eldan, a vice president at Luxembourg-Pamol, said her company had the scientific literature scoured and found 300 studies published since 2007 that the EPA had not included in the draft.

"If the report is not up to date, a risk assessment cannot be based on that," Eldan said in an interview. "We mentioned that because this is the one inarguable detail. You can argue about toxicity. You can argue about risk assessment. You can't argue about 300 publications that are missing from the list of references."

Grizzle added, "I think it's safe to say that the missing 300 studies, if you will, really exposed EPA to accusations from congressmen and stakeholders that they were cherry-picking the data."

In August 2010, 15 Republicans in the House and Senate made that very argument in a letter to then-EPA Administrator Lisa Jackson:
"We are informed that there are nearly 300 studies in the scientific literature on arsenic published since 2007 that were not included in the agency's evaluation. We find that troubling and are concerned that this could allow critics to conclude that the agency is 'cherry-picking' data to support its conclusions."

After reading the letter, Michael Hansen, a senior scientist at Consumers Union who has followed the arsenic review closely, said, "This is a really dishonest couple of sentences ... That's because the [EPA] document was written in early 2008, and the only reason the public is seeing it [in 2010] is because OMB sat on it."

"It's not cherry-picking the data. When the document was written, those studies hadn't been published yet," he said.

Yet the missing publications ultimately became the rationale for Congress to derail the EPA's assessment. In July 2011, language appeared in a House Appropriations Committee report ordering the EPA to take no action on its arsenic assessment and turn the job over to the National Academy of Sciences. The report instructed the academy to include "the 300 studies in the published scientific literature EPA failed to review for its 2010 draft assessment."

U.S. Rep. Chellie Pingree, D-Maine, speaks at a campaign stop for President Obama at Southern Maine Community College in 2012.
Robert F. Bukaty/AP

Committee reports explain how to implement a bill. Government agencies could ignore them, but they seldom do, for fear of angering congressional leaders who control funding. Burying language in a report — as opposed to the bill itself — was the same technique once used for earmarks. Steve Ellis, vice president of Taxpayers for Common Sense, a nonprofit group that closely monitors the Appropriations Committee, said rank-and-file members of the House cannot strike or amend language in a report. In fact, he said, only a couple of lawmakers in leadership would likely know who put the language in the report.

Rep. Chellie Pingree, a Maine Democrat on the subcommittee that oversees EPA funding, said she has no way of knowing who is responsible for trying to kill the arsenic assessment.

"It's happening more and more in this Congress that we see less and less of what goes on behind the scenes, that members aren't informed until the last minute," she said. "So things like this, major policy changes like this, can happen somewhat in the dark of the night with very little information to the public."

Congress' arsenic concerns echoed industry's

Congressional letters and reports questioning the EPA's process for arsenic echoed one industry group's concerns. Among the points made by the Organic Arsenical Products Task Force, and later, Congress include whether a Taiwanese study could be relied upon and whether a working group ignored a list of nearly 300 studies attached to a letter from the group.
arguments:

- Docket not reviewed
- Taiwanese study
- 300 missing studies
- Too short a time

Public comment to EPA by pesticide company exec. (pg. 4)
Letter from Congress elaborating on concerns (pg. 1)

Rep. Mike Simpson, R - Idaho.
simpsonforcongress.com

So, who did it? All the evidence from the Center's investigation pointed to one congressman: Mike Simpson of Idaho.

Simpson was one of the Republicans who signed the letter to the EPA administrator complaining about the missing 300 studies. He was the chairman of the subcommittee that controlled funding for the EPA, where the language first appeared. He was also a member of another committee where the language surfaced again in a different report. He even asked the EPA administrator about arsenic at a subcommittee hearing.

Simpson, who worked as a dentist and state legislator before entering Congress, is a frequent critic of the EPA. But in the 2012 and 2014 election campaigns, he has been portrayed as too liberal by Tea Party candidates funded by the right-wing Club for Growth.
In a brief interview outside his Capitol Hill office, Simpson accepted credit for instructing the EPA to stop work on its arsenic assessment.

"I'm worried about drinking water and small communities trying to meet standards that they can't meet," he said. "So we want the Academy of Science to look at how they come up with their science."

Simpson said he didn't know that his actions kept a weed killer containing arsenic on the market. He denied that the pesticide companies lobbied him for the delay.

But lobbyist Grizzle offered a different account.

"I was part of a group that met with the congressman and his staff a number of years ago on our concerns," Grizzle said, adding that there were four or five other lobbyists in that meeting but he couldn't remember who they were.

Other organizations that disclosed lobbying the EPA and Congress on the agency's arsenic evaluation were the U.S. Rice Federation; the Mulch and Soil Council; the Association of California Water Agencies; and the National Mining Association, including the mining companies Arch Coal and Rio Tinto.

Grizzle began making donations to Simpson's re-election campaign in January 2011, a few months before Simpson took action to delay the arsenic assessment. Since then, Grizzle has given a total of $7,500. That's more than he's given in that time to any other candidate.
Asked if the contributions were made in exchange for the delay, Grizzle said, "I don't see a connection. I've been a friend and supporter of Congressman Simpson for a long time."

When Simpson was asked if he was aware of the donations, he terminated the interview, saying, "I have no idea. But I've got a hearing."

Industry playbook

The National Academy of Sciences was created during the Civil War to provide objective advice from the nation's most highly regarded scientists. In 1999 and 2001, the academy twice reviewed the EPA's analysis of arsenic and concluded it badly underestimated the risk. The EPA's draft that has been delayed was built in part off the academy's critique.

Taking scientific assessments out of the hands of the EPA and giving them to the academy has become a tactic to delay regulations, said Charles Fox, a former EPA assistant administrator who oversaw the development of a new drinking water standard for arsenic.
"The standard playbook that industry uses first begins with questioning the science, and they can question the science in any one of a number of different forms," he said. "There is a scientific advisory board at EPA. There's the National Academy of Sciences."
But endless delays to perfect the science can jeopardize public health, Fox said.

"We always as regulators had to do our best to make decisions based on the best available science we had at the time. Science will always improve and you can always revisit that decision down the road, but fundamentally we have an obligation to protect public health in the environment, and that decision needs to be made on the best science that you have today."

In a letter last October telling buyers that the EPA had lifted its ban for at least three years, the MSMA manufacturers said in a joint statement that they "fully expect[] the NAS review to result in a less stringent risk value for human exposure to inorganic arsenic."
If so, the companies said, they are confident the threat of a ban will be lifted permanently and the EPA may even allow other uses of MSMA.

The two manufacturers of the herbicide are still trying to influence the scientific assessment. The National Academy held a meeting in April 2013 to review the science on arsenic. It invited 14 scientists to give presentations. Two of those scientists are funded by Drexel and Luxembourg-Pamol, which lobbied Simpson to delay the EPA.

The academy doesn't require presenters to disclose their financial ties; some choose to do so and some don't. Neither of the scientists funded by the pesticide companies disclosed their ties at the meeting.

Dr. Samuel Cohen, a professor at the University of Nebraska College of Medicine, told the panel that inorganic arsenic doesn't cause cancer or any other diseases in people below a certain threshold dose, which he suggests is substantially higher than the current drinking water standard. Cohen has been funded by the MSMA manufacturers for more than a decade, according to disclosures in published articles.

Barbara Beck, who works for Gradient, a scientific consulting firm often hired by industry, also gave a presentation without disclosing her ties.

Eldan, with Luxembourg-Pamol, acknowledged that both scientists are paid by her company. Beck prepared a 32-page report on the EPA's arsenic assessment. Eldan said that Beck and Cohen disclose their ties in published articles in scientific journals. In some cases, Eldan, a scientist herself, is listed as a co-author.

Cohen said in an email that he disclosed his funding in published articles that he provided to the academy. Records show that Cohen sent the academy three articles that listed funding only from the "Arsenic Science Task Force," with no further explanation about the task force.

Beck said, "Although I have done work for the Organic Arsenical Products Task Force [composed of the two pesticide companies], my presence and presentation at the April 2013 meeting were funded wholly by Gradient .... At both meetings, I am solely responsible for my comments."

Joseph Graziano, who chairs the National Academy of Sciences panel on arsenic, said he hadn't realized that Beck and Cohen were being funded by the pesticide companies when they spoke at the workshop. "I was not aware of that," he said, "and I don't think the committee was aware of it."

Congress rescues the formaldehyde industry

This is not the first time Congress has pressured the EPA to hand over science on toxic chemicals to the National Academy. In 2009, Sen. David Vitter, a Republican from Louisiana, held up the nomination of a top EPA official as leverage to force the agency to have the academy review the risks of formaldehyde.

The World Health Organization's International Agency for Research on Cancer and the National Institute of Health's National Toxicology Program both say that formaldehyde can cause cancer. The EPA was preparing to say the same.

Yet the agency ultimately relented to Vitter's demand. After months of review, the academy criticized the IRIS draft on formaldehyde for being repetitive, poorly organized and failing to clearly present all the evidence of its findings. The panel recommended the EPA redo the draft to be more clear and concise. Recognizing that the EPA was having a problem in completing assessments, the academy said it wasn't calling for a delay.

Soon, however, the formaldehyde industry was turning to Congress to help it delay the assessment. Right next to Simpson's language in the committee report about delaying the arsenic assessment was another set of instructions to the EPA. This time, IRIS was told to apply the academy's recommendations on formaldehyde to all ongoing and future assessments. When asked if he requested the language, Grizzle acknowledged only that he was one of the lobbyists for the Formaldehyde Council, an arm of the industry.

The EPA said in a report to Congress it won't start all its assessments over from scratch, but it will try to incorporate the academy's recommendations. As a result, the 47 pending reviews have been further delayed.

IRIS Director Vincent Cogliano said the changes will lead to more rigorous assessments that should have an easier time getting through peer review. When asked how IRIS responds to political pressure, he said he had little control over that.

"We're doing our best to keep our assessments focused on the science," he said. "What happens after that is not part of the IRIS process."

'It's not their right'

Eldan said people shouldn't be worried about her company's weed killer.

"To be honest, we believe that this is a good product, that it does not pose a concern to health and the environment," she said.
Clearing weeds from the sides of highways can be a safety issue, she said, because tall plants can block vision. Even on golf courses, there are safety concerns, she said.

"The weeds have a tendency to spread. If you don't use herbicides, it's not only one weed. They can cover the golf course," Eldan said. "The players can stumble on them."

Wendy Brennan and her granddaughter, Madelyn Begin.
Amy Temple

Madelyn, left, and Abigail Begin. Madelyn is leaning on the well that contains arsenic.
Amy Temple

Meanwhile, in Maine, Wendy Brennan worries about all the years her family was drinking arsenic-tainted water.

"I know a lot of people around the area that have had cancer, and so you always think, 'Jesus, that's going to be my kids. It's going to be me or my husband,' " Brennan said.

Her congresswoman, Pingree, also worries about her constituents.

"When you have a toxic chemical in the environment that could be affecting child development or people who could eventually be contracting cancer from their exposure to this, we shouldn't be delaying," Pingree said.

She fears that after the National Academy of Sciences completes its review, the pesticide companies will find another delaying tactic.
"That's the sad part; there's nothing to stop Congress from finding another roadblock to delay," Pingree said. "Congress can say, 'Well, here's another 200 studies, you better review them.' "

Brennan doesn't understand why there's a need to wait.

"If they've already got some proof that it's 17 times more potent, you'd think they'd want to get the information they had out and then continue to explore scientifically more," she said.

"We need to know what's going on with our drinking water. If somebody wants to not let us know because they want to keep some pesticides making money for five more years ... it's not their right. It's not their body. It's not their decision."

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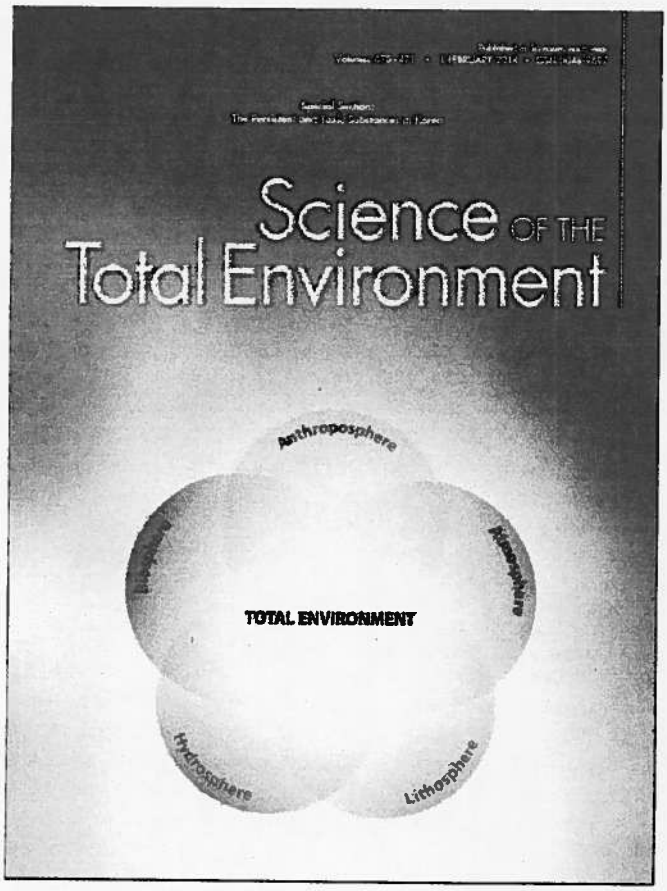

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Short Communication

A web-based tool to engage stakeholders in informing research planning for future decisions on emerging materials☆

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HIGHLIGHTS

- A web-based, interactive decision support tool was piloted for emerging materials.
- The tool (CEAWeb) was based on an established approach to prioritize research gaps.
- CEAWeb facilitates multi-stakeholder prioritization of research gaps.
- We provide recommendations for future versions and applications of CEAWeb.

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ABSTRACT

Prioritizing and assessing risks associated with chemicals, industrial materials, or emerging technologies is a complex problem that benefits from the involvement of multiple stakeholder groups. For example, in the case of engineered nanomaterials (ENMs), scientific uncertainties exist that hamper environmental, health, and safety (EHS) assessments. Therefore, alternative approaches to standard EHS assessment methods have gained increased attention. The objective of this paper is to describe the application of a web-based, interactive decision support tool developed by the U.S. Environmental Protection Agency (U.S. EPA) in a pilot study on ENMs. The piloted tool implements U.S. EPA's comprehensive environmental assessment (CEA) approach to prioritize research gaps. When pursued, such research priorities can result in data that subsequently improve the scientific robustness of risk assessments and inform future risk management decisions. Pilot results suggest that the tool was useful in facilitating multi-stakeholder prioritization of research gaps. Results also provide potential improvements for subsequent applications. The outcomes of future CEAWeb applications with larger stakeholder groups may inform the development of funding opportunities for emerging materials across the scientific community (e.g., National Science Foundation Science to Achieve Results [STAR] grants, National Institutes of Health Requests for Proposals).

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Abbreviations: CEA, comprehensive environmental assessment; CEAWeb, CEA web interface; CEAPrioritize, CEA spreadsheet tool; ENM, engineered nanomaterials; E-RRF, element-risk relevance factor pair; HERO, Health and Environment Research Online; MCDA, multi-criteria decision analysis; MWCNTs, multiwalled carbon nanotubes.

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1. Introduction

1.1. Decision support approaches for emerging materials

Data gaps and scientific uncertainties associated with the behavior of emerging materials can limit our ability to quantify environmental health and safety (EHS) risks, resulting in inadequate information for risk managers. Risk management of emerging materials, such as engineered nanomaterials (ENMs), can benefit from innovative methods that: 1) incorporate various aspects of EHS risks, 2) identify sources of uncertainty and data gaps, and 3) consider stakeholder preferences. To demonstrate the development and pilot testing of one such innovative method, this short communication focuses on ENMs as an example class of emerging materials.

In the case of ENMs, researchers have begun to develop assessment tools and approaches that may help guide decisions about the prioritization of research gaps, preferred methods of ENM synthesis, or identification of ENMs that present the "most" or "least" potential risk based on stakeholder values (e.g., Linkov and Seager, 2011; Tervonen et al., 2009; U.S. EPA, 2012b). Many of these methods incorporate components (e.g., product life cycle framework, exposure and hazard considerations, prioritization) recognized as important for moving toward risk analyses and subsequent risk management of ENM (NRC, 2012; OECD, 2012). Yet as noted in a recent review, available approaches for ENM risk analysis often focus on potential risks in occupational settings and have generally not been applied to a wide variety of ENM (Grieger et al., 2012). Both of these shortcomings suggest that the field would benefit from an approach to more quickly evaluate multiple ENM-types in the context of future environmental (including occupational) risk analyses and risk management. Moreover, recent guidance from the National Research Council and others notes the importance of structured approaches to 1) better connect the identification of research gaps with future assessment efforts, and 2) engage stakeholders throughout the risk assessment process (Abt et al., 2010; NRC, 2011; U.S. GAO, 2013). To address these gaps in current approaches (i.e., relatively rapid evaluation, inclusion of environmental and occupational data, connection of research gaps to future assessments, stakeholder engagement) a pilot tool was developed based on an existing approach, comprehensive environmental assessment (CEA).

1.2. The CEA approach

The U.S. EPA CEA approach facilitates a *process* to collect available information within a *framework* and consider expert stakeholder input in decision making on complex EHS problems (Powers et al., 2012). CEA aims to (i) link research planning, risk assessment, and risk management; (ii) structure and integrate complex information from multiple analytical techniques and approaches (e.g., LCA, risk assessment); (iii) engage diverse perspectives to inform near-term or long-term risk management efforts; and (iv) support iterative risk assessment approaches and adaptive risk management through prioritization efforts (Powers et al., 2012). While other risk-based approaches (e.g., life cycle assessment [LCA], human health risk assessment [HHRA]) or decision support approaches (e.g., MCDA, expert elicitation) can support any one of these objectives, CEA adds an approach to manage information from existing assessment and decision support tools (i.e., a meta-assessment) to the decision maker's tool box (Powers et al., 2012). U.S. EPA has recently applied CEA to several types of ENM (U.S. EPA, 2010, 2012a,b). The core components of each CEA application included (1) draft case study documents that use the CEA framework (conceptualized here in Fig. 1)

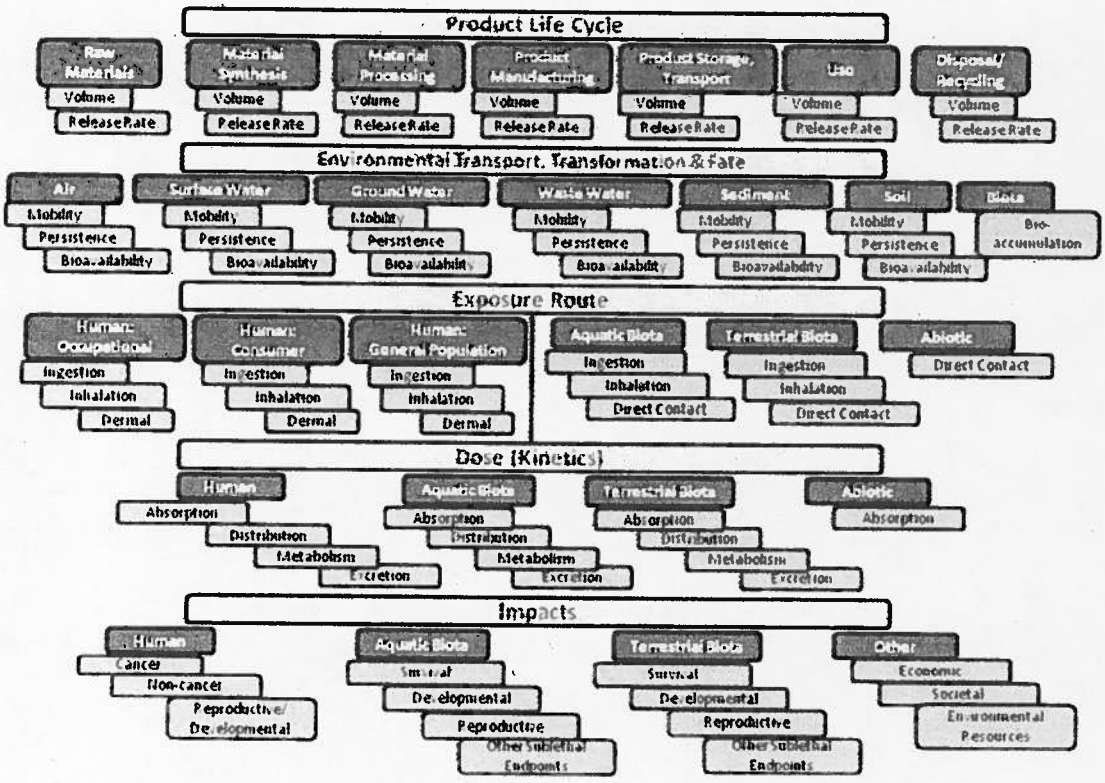

Fig. 1. Detailed CEA framework that provides more granularity to the previously developed framework (see U.S. EPA, 2012a,b). Source RTI International (2012).

to organize compiled information on the ENM of focus (e.g., multiwalled carbon nanotubes [MWCNTs]), and (2) the engagement of expert stakeholders, a large portion of which involved face-to-face interactions. The first component helps to ensure that information pertinent to a wide range of domains (e.g., product life cycle, exposure in human or ecological populations, economic or social impacts) is conveyed to expert stakeholders. The CEA case study documents thereby support the consideration of issues (e.g., aggregate and cumulative exposures, environmental justice) that are less frequently included in other assessment approaches (e.g., LCA, HHRA) during the structured stakeholder engagement within CEA.

1.3. CEA web interface (CEAWeb)

Active stakeholder involvement is important to inform EHS decision making (Jones, 2009; NRC, 2008); however, time, budget, and environmental considerations can impede face-to-face stakeholder interactions. To address these challenges, a web-based decision support tool was developed ("CEAWeb") that employs a collective judgment method to gather expert input; this tool was evaluated during a pilot study on MWCNTs in flame-retardant coatings applied to upholstery textiles. Assumptions that underlie this pilot work include the following. First, that a relatively small group of expert stakeholders can demonstrate the utility of a tool intended to be used with a larger stakeholder group. Second, that limiting interaction between expert stakeholders to the review of written comments and data representing the group's collective response would more clearly show the potential value and limitations of a web-based stakeholder engagement approach compared to face-to-face engagement approaches.

The pilot resulted in two outcomes: 1) a demonstration of this web-based decision support tool to facilitate iterative stakeholder engagement in the CEA approach, and 2) a set of example research priorities identified by expert participants using the tool. The research priorities identified through the web-enabled CEA process are briefly compared here to priorities identified through a similar CEA process that also included a more traditional face-to-face workshop.

2. Materials and methods

A web-based prioritization tool, CEAWeb, was developed by U.S. EPA as described in the supplementary material. CEAWeb is based on a spreadsheet-tool, CEAPrioritize (RTI International, 2012). CEAPrioritize was developed[1] and used in a parallel prioritization effort that included two rounds of remote prioritization (i.e., experts accessed and completed the tool without meeting), followed by a third prioritization round during a face-to-face workshop independently conducted by RTI International and funded by U.S. EPA (RTI International, 2012). Both prioritization processes (remote prioritization only [CEAWeb] and remote prioritization plus face-to-face [CEAPrioritize]) used the same draft CEA case study document on MWCNTs (hereafter MWCNT draft case study document) to provide experts with common background information on MWCNTs (U.S. EPA, 2012a). Similarly, in both prioritization processes participants with comparable distributions of expertise and sector perspectives were recruited; however, limited budget resources in the CEAWeb pilot restricted the number of participants, resulting in fewer areas of expertise in the pilot (CEAWeb: 8 and 6 participants in Rounds 1 and 2, respectively; CEAPrioritize: 32, 28, and 13 participants in Rounds 1, 2 and 3, respectively). Approximately half of the participants selected to pilot CEAWeb were also participants in the prioritization process that utilized CEAPrioritize in conjunction with the RTI International face-to-face workshop; this allowed for direct comparison of the CEAPrioritize plus face-to-face and CEAWeb in ranking research priorities. Though not large enough for statistical evaluations, the objective of this comparison was to better understand the implications of using CEAWeb in lieu of face-to-face interaction when identifying research priorities. CEAWeb can be used to inform research planning decisions for any material or group of materials; however, it is applied here to MWCNTs as a test case. For details on selecting the test case see U.S. EPA (2012a).

To pilot the CEAWeb tool, RTI International, a contractor for U.S. EPA, independently selected scientific experts based on their areas of expertise (e.g., chemistry, fate and transport, toxicology) and sector areas (e.g., academia, industry, government). The overall goal in the selection process was to include a diverse range of both technical and sector perspectives in the pilot (see the supplementary material for additional details). Participants used CEAWeb, hosted by U.S. EPA on a secure online platform, to rate research areas based on the CEA framework.

Participants accessed the CEAWeb home page on the U.S. EPA's Health & Environment Research Online (HERO) website (http://hero.epa.gov/). The home page provided background information on CEA and the web-based pilot, along with links to the MWCNT draft case study document and the MWCNT-specific portion of the prioritization tool (CEAWeb—MWCNT). After accessing the home page participants were instructed to watch an introductory webinar on the prioritization process and review the MWCNT draft case study document for background information (U.S. EPA, 2012a). A user's guide with step-by-step instructions for completing CEAWeb was also made available for participants. For this pilot, two rounds of prioritization were completed with CEAWeb.

In each round of prioritization experts rated research areas across a detailed version (Fig. 1) of the existing CEA framework (Powers et al., 2012) according to their level of "Importance" to risk assessment efforts and "Confidence" in the availability and utility of current information to

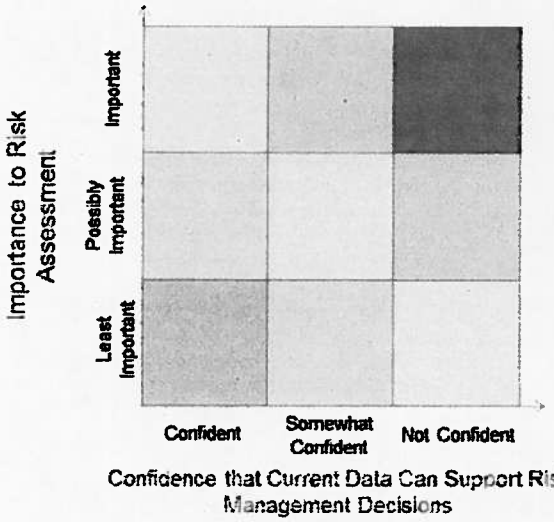

Fig. 2. Prioritization matrix. In the prioritization process employed in the CEAWeb pilot, research areas (i.e., E–RRF pairs in Fig. 1) that experts rated as "Important" to risk assessment and "Not Confident" that existing data can support risk management decisions were deemed high priority research areas (RTI International, 2012). Colors in the figure indicate the priority level associated with each combination of importance/confidence (i.e., red denotes the highest priority for research, followed by orange, yellow and green, respectively).

[1] The software tool was developed using Microsoft Excel by RTI International in an EPA-funded project.

support risk management decisions (Fig. 2). Specifically, participants rated research areas in the form of "Element–Risk Relevance Factor" (E–RRF) pairs within the detailed CEA framework (e.g., "Air" is an element associated with the risk relevance factor "Mobility" within environmental transport, transformation, and fate in the CEA framework, see Fig. 1). Each step that participants carried out to complete the rating process is listed in the supplementary material. Briefly, each participant rated each element based on its importance to consider in future risk assessments of MWCNTs in flame-retardant textiles (i.e., ratings were "Important", "Possibly Important" or "Least Important"). For those elements that a participant rated as "Important" they were asked to rate the element paired with its respective RRFs (Fig. 1) based on the same scale of importance. They also rated each E–RRF on their level of confidence in the availability and utility of current data to support future risk management decisions for MWCNTs in flame retardant textiles (i.e., confidence ratings were "Confident", "Somewhat Confident" and "Not Confident") (Fig. A.1). Prior to completing each prioritization round, participants were instructed to review their ratings prior to submitting their final answers.

After each round of prioritization, all participant ratings were compiled and tallied for each E–RRF. Each E–RRF pair was then assigned a bin in the prioritization matrix (Fig. 2) based on the most frequently selected rating for "Importance" and "Confidence". Those areas (i.e., E–RRF pairs) that experts most commonly rated as both most important to risk assessment and had the least confidence in the data to support risk management decisions (i.e., red bin in Fig. 2) were then identified as "high priority research areas". See the supplementary material for more details related to the methodologies and terms used in the prioritization process.

Participants were instructed to complete the first round of prioritization using CEAWeb (Round 1), view and compare the results of the group with their own by using a series of bar charts and tables, and then complete the second and final prioritization round using CEAWeb (Round 2). The output from Round 2 formed the final results generated from the pilot prioritization process. Participant feedback on the prioritization process and the use of the CEAWeb was also solicited.

3. Results

3.1. Demonstration of CEA web-based stakeholder engagement

CEAWeb was developed to facilitate the prioritization of research gaps in areas where new data could make future risk assessments more scientifically robust, and subsequently inform risk management decisions involving emerging materials. Experts in the ENM field with diverse sector and technical perspectives agreed to participate in a pilot study using CEAWeb with a specific material, MWCNT (CEAWeb–MWCNT, shown in Fig. 3).

In total, eight participants utilized CEAWeb–MWCNT to complete the first prioritization round (Round 1) and six participants completed the second prioritization round (Round 2)[2]; four of the participants who completed Round 2 also participated in the prioritization process using CEAPrioritize and a face-to-face workshop. In the case of the CEAWeb pilot, Rounds 1 and 2 results (Tables A.2 and A.3) were conveyed to participants using a series of bar charts and tables (e.g., Fig. A.2) to allow the experts to become familiar with how other experts perceive research priorities without face-to-face discussion. The primary outcome of this pilot study was the demonstration of how a web-based tool can facilitate the iterative engagement of expert stakeholders to prioritize research efforts.

[2] The initial number of participants was small due to resource constraints and the pilot nature of this project. Two participants did not complete the second round due to competing priorities. See the supplementary material for greater detail on participant selection.

Expert reviews of CEAWeb were generally positive, with mostly positive or neutral feedback to all ten questions related to the tool posed to reviewers (Table 1). With regard to CEAWeb as a tool, the experts identified website accessibility and download speed consistency as two areas for improvement. With regard to the prioritization process, the experts had differing opinions on areas for improvement. For example, some experts suggested reducing the number of areas (e.g., E–RRFs pairs) to rate during each round of prioritization, while others noted that the E–RRF pairs included in the current version of the tool allowed them to more easily consider information outside their field of expertise. Participants also identified reducing the amount of time required to complete the prioritization process as another areafor improvement, including (1) decreasing the total number of prioritization rounds, (2) allowing responses in one area to be applied to another, and (3) retaining data from one round to the next so that participants did not need to re-enter responses. In addition, some experts noted that greater interaction with other participants between rounds would improve the prioritization results. Finally, one expert noted the importance of identifying inter-relationships between different areas of the CEA framework (e.g., "Air–Mobility" relates to "Human Occupational-Inhalation"), something that is not currently supported by CEAWeb.

3.2. Research areas identified through piloting CEAWeb

Research priorities obtained in this pilot of CEAWeb—MWCNT were in general agreement with those identified using CEAPrioritize and a face-to-face workshop. As shown in Fig. 4, most priorities from both processes (i.e., with and without a face-to-face meeting) relate to MWCNT release across the product life cycle and human exposure or health impacts (Fig. 4; Supplementary Tables A.3 and A.4). Yet, several key differences were observed. For example, experts using CEAWeb alone identified a smaller number of priorities (13) compared to those that participated in a face-to-face discussion (24). Experts using CEAWeb also tended to have higher importance and confidence ratings for research priorities compared to those participating in the face-to-face workshop (Fig. 4). Additionally, "other" impacts (i.e., social, economic, environmental resources) identified as priorities through face-to-face discussion, were not identified by experts through the exclusive use of CEAWeb. Experts also provided specific research questions for priority research areas (Table A.5). These example research questions for MWCNTs demonstrate how CEAWeb can facilitate engaging stakeholders in moving from identifying broad research areas to informing more detailed research planning.

4. Discussion and conclusions

The successful pilot of CEAWeb to prioritize specific ENM research needs demonstrates several advantages compared to non-web based prioritization tools (e.g., face-to-face workshops, desktop software tools). Previous efforts to engage experts in identifying and/or prioritizing research gaps for ENM have relied primarily on expert elicitation (e.g., Morgan, 2005; Wardak et al., 2008) or workshops and committee discussion (e.g., NNI, 2011; NRC, 2012). CEAWeb builds on these efforts by incorporating a structured methodology to ensure that each expert has equal input in the outcome (i.e., identified research priorities) and thus avoid outcomes that may represent the perspective of some technical disciplines or sectors more than others. In addition, previous efforts generally rely on face-to-face interaction, which can limit the number of individuals involved in the process due to time, travel, budget, or other constraints. Specific advantages of CEAWeb include:

- supporting virtual interactions among, theoretically, an unlimited number of participants;
- allowing participants to manage their time individually, thereby increasing the likelihood, and potentially, the quality of participation by increasing convenience;

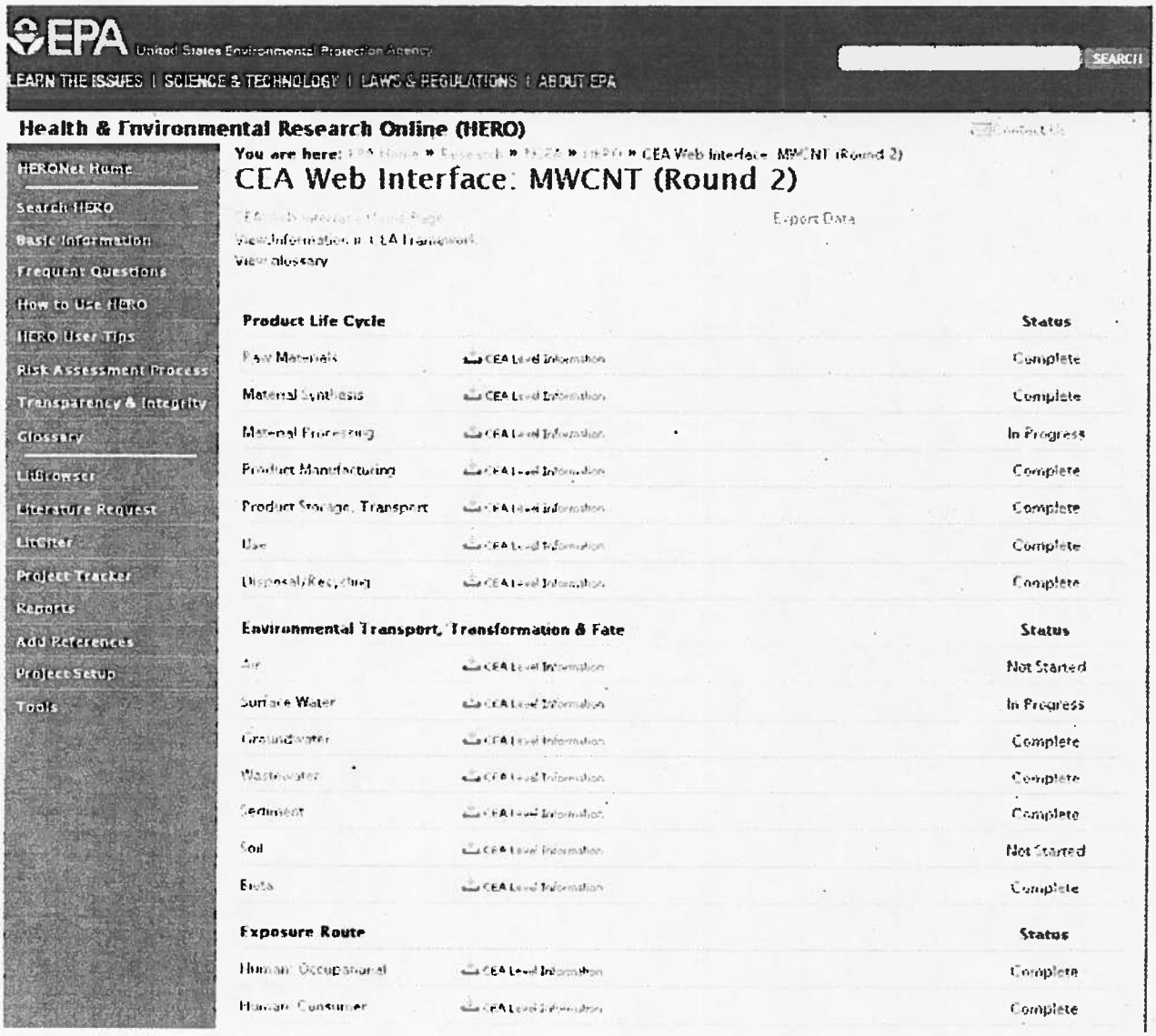

Fig. 3. CEAWeb–MWCNTs. The portion of CEAWeb that participants used to rate research areas for MWCNTs.

- providing a dynamic interface so that content is based on the user's responses (e.g., status updates, content-specific warning messages for incomplete responses, final check prior to submission [data not shown]);
- increasing stakeholder input on research planning for a variety of chemicals or materials since multiple iterations of the tool could be run simultaneously (i.e., multiple groups of experts could evaluate different chemicals or materials at once); and
- promoting real-time feedback on the tool by the user community, allowing for continual improvement as new versions are produced.

Nevertheless, several features/functions were identified for development in subsequent versions of CEAWeb (see Table 1 and supplementary material), including:

- employing a pre-prioritization step in which participants take part in a structured discussion to agree on a subset of areas in the CEA framework to focus on, which would narrow the scope of prioritization for a given chemical or material;
- providing background information on E-RRFs to clarify the types of considerations in each (e.g., listing potential abiotic resources affected by exposure to a material to clarify "Abiotic-Direct Contact" under "Exposure Route" [Fig. 1B]);
- facilitating the identification of inter-relationships between areas of the CEA framework;
- allowing structured discussions of results (e.g., use of social networking mechanisms) and continuing to improve the user experience;
- presenting results in terms of the variation of responses in addition to providing an overall group rating;
- emphasizing how results will be used to inform research planning to encourage scrutiny of initial group results; and
- providing dynamic access to background information by directly linking to other existing tools and databases to use as reference material (e.g.,

http://webnet.oecd.org/NanoMaterials, http://icon.rice.edu/report.cfm) in lieu of a static draft case study document.

Results of this study show that research priorities identified by engaging stakeholders using a web-based tool are generally similar to those identified through a process that includes an additional face-to-face component. Notably, similarities in results may stem, in part, from 1) expert stakeholders in both processes reviewed the same background material (i.e., U.S. EPA, 2012a), and 2) some experts participated in both processes. While these factors combined with a small sample size prevent validating any assertions statistically, the results suggest that with some modifications to facilitate user interactions in CEAWeb, comparable results could be achieved using the web-based tool alone. Future efforts could build on these results by developing

Table 1
Summarized responses from experts participating in CEAWeb pilot study. The number of responses authors identified as "Generally Positive", "Neutral", or "Generally Negative" (Columns) is denoted for each question participants responded to in the CEAWeb pilot (rows). Gray shading denotes the column with the majority of responses. In instances of a tie both columns are shaded gray in the appropriate row. Full responses and their categorization as "positive," "negative," or "neutral" are shown in the supplementary material.

Question	Responses from participants			
	Generally positive (No.)	Neutral (No.)	Generally negative (No.)	Summarized feedback
1. Do you have specific suggestions for additional information that would be helpful to include on the CEA web interface home page? Alternatively, is there information that could be removed from the page?	3	1	2	• Improve CEA website interface (speed, password resets). Add dates after milestones • Instructions were clear and helpful • Case study section of webpage is crowded. • Simplify right-side by using collapsible categories of information • Previous case study documents do not need to be directly accessible
2. Did you refer to the user guide prior to accessing the web interface? If so, do you have specific suggestions for additional information to include in the CEA web interface wser guide document?[a,b]	5	1	2	• Information is useful & necessary but after the first round, the web interface is self-explanatory/ easy to use • Move step-by-step instructions (Section 3) to front of user guide, with full document as a resource • Easy to miss where the user guide is on the web page, one has to scroll down too far to find it
3. Do you have specific suggestions that could improve the CEA web interface: MWCNT page (e.g., ways to access the draft case study document, selection of elements, accessing the glossary)[c]	4	1	3	• CEA web interface: MWCNT is a very practicable tool, good access to documents and glossary • Decrease download time for portion of documents used as reference for each element • The case study is also listed too far down on the right side; move it front and center on the CEA website. • Consider only one round of rating; participant was more likely to select "Possibly Important" to follow group/ avoid selecting IFs • Don't clear responses from the 1st Round • Allow information to be copied from one portion of rating process to another (e.g., selecting similar factors that might influence risk of persistence in waste water and ground water)
4. Do you have specific suggestions to improve the format or usability of pages that allow you to rate elements and element–risk–relevance factor pairs, as well as select influential factors?[d,e]	5	0	4	• Compared to the non-web based approach, paring process seemed to move smoothly. • Particularly like easy access to the part of the case study that was relevant to a given set of questions. • Rating process needs to facilitate identifying inter-relationships between areas of the framework • The selection of the influential factors is not easy, because they are not always relevant to the elements in question. Allow Round 1 responses to be revised in Round 2 rather than starting over • Results need to be more clearly presented on Home Page • The outcome of the prioritization process is not intuitive
5. On a scale of 1 to 10, please rate how straightforward and easy the CEA web interface as a whole was to use in this prioritization process (1 = very difficult, 10 = extremely straightforward & easy). For any rating below 10, please provide specific improvements that would change your rating[f,g].	6	0	4	• As compared to other tools, the CEA Web Interface is very straightforward and practicable. • Reasonably easy to click through the boxes. • Website was much easier to fill out the influential factors since they are all on one screen; it was much easier to scroll down a web page than across a complex Excel spreadsheet. • Warning boxes became annoying after the first time (particularly for responses that weren't required) • Rating process needs to better distinguish between having confidence that something isn't important, so not much info is required versus when something is important and requires much more information (detail) and thus should be retained for further analysis • Reduce amount of introductory material & information on home page • Reduce time to complete rating process • Website speed needs to be consistently high

(continued on next page)

Table 1 (*continued*)

Question	Responses from participants			
	Generally positive (No.)	Neutral (No.)	Generally negative (No.)	Summarized feedback
6. On a scale of 1 to 10, please rate how the CEA web interface compares to using a spreadsheet tool (e.g., in Microsoft Excel) to conduct a rating process (1 = no difference between a spreadsheet and the Web Interface, 10 = using a spreadsheet is completely different than the web interface). Please briefly explain your rating by specifying whether the difference, or lack thereof, is preferable[h,i]	5	0	3	• It is quite different from the other tools, & much preferred. • Some parts which were quite different in ways that were better and worse. • Web interface is more suitable for working in influential factors and pairing processes. • Could go from one element to the next via different web pages instead of having all of them for a particular section on the same page. • Reviewing answers before submission seemed also easier in web based approach. • Pare down information to review & rate to improve confidence in rating • Discussion with diverse subject matter colleagues is critical • Consider enabling information from one area of rating process to be copied over to another portion (e.g., selecting similar factors that might influence risk of persistence in waste water and ground water) • Consider enabling rating on a local copy and transferring data to website for instances when an internet connection isn't available • Web tool is much more preferable than Excel tool for
7. Are there additional elements or risk relevance factors that would be beneficial to include in the detailed CEA framework for future applications of this approach to other chemicals, materials, or technologies?[j]	3	1	3	• Reduce number of elements & risk relevance factors and allow more identification of the interactions between pairs • Approach is applicable to other materials; biomaterials in biomedical & industrial sectors might be areas to apply the approach • Revise "inhalation for aquatic organisms" • Include links to literature reviews of CNTs
8. Did you find that including MWCNT-specific influential factors allowed you to add more detail to explain what could be important to research about the areas of the CEA you prioritized? Do you have specific suggestions about how the influential factor portion of the prioritization process could be improved, or about additional influential factors that would be beneficial to include?[k]	4	1	3	• Greater granularity is needed so that factors aren't considered in abstract • Adapt list of influential factors for each specific element • Having a list of factors to consider provides a quick overview of points to think of in prioritizing • Bio–physico–chemical variables captured in MWCNT influential factors capture the most relevant ones • Influential factors added more detail in some cases but added to time required to complete process • Influential factors didn't seem to influence the outcome • Remove influential factors to reduce time to complete the process • Influential factors added a high degree of granularity • Influential factors prompted consideration of angles that a participant wouldn't have thought of • Addition of influential factors didn't increase detail the in responses
9. Are the results of each prioritization round clearly conveyed? Do you have specific suggestions for improving how results are reported?	4	0	2	• Results were clearly presented • Bar graphs are not particularly informative • Focusing analyses on variation in responses would more useful • Reviewing results was time consuming but information was useful • Figures appeared somewhat crowded and confusing • Providing overall summary before detailed answers facilitated finding detail on particular elements of interest • Decrease sizes of colored boxes and increase font size within boxes to improve presentation of results

Table 1 (*continued*)

Question	Responses from participants			
	Generally positive (No.)	Neutral (No.)	Generally negative (No.)	Summarized feedback
10. Did you change your responses in Round 2 of prioritization after reviewing the results of Round 1 of prioritization? Please briefly explain why or why not?	1	4	1	• Responses changed somewhat but the most useful activity is discussion with experts in other subject matters • Recommend reducing number of rounds • Recommend using just one round. The first response is most likely the correct response. • Responses in the second (or third) rounds are not developed with as much focus and rigor as the first time around. • Re-assessed opinion, went back to background information, and changed response in a few instances when Round 1 response differed completely from the group • Little to no change in responses since initial responses were based on literature and discussion with experts in workshop • Changed some responses from Round 1 to 2, particularly those where the rest of the group rated an element differently • Moved rating closer to consensus rating if convinced by "Why" responses of others • In-person meeting strongly influenced second round responses • Did not change responses in areas of own expertise, but was informed by others' responses and made minor changes in other areas
11. What are the top three detailed research questions that you feel should be prioritized to enable future comprehensive environmental assessments of MWCNT flame-retardant coatings applied to upholstery textiles, in support of risk-based decisions?	N/A[i]	N/A	N/A	See Supplementary Table 5.

[a]One participant responded "I did not refer to the user guide since I had previously completed the Excel version.", which is considered a neutral response.[b]Two participants responded with both positive and negative comments, which were marked in both columns.[c]Two participants responded with both positive and negative comments, which were marked in both columns.[d]One participant had a positive response for element and element-risk-relevance factor pairs but a negative response for influential factors; the response is documented in both the positive and negative columns here.[e]Three participants responded with both positive and negative comments, which were marked in both columns.[f]One participant rated the web tool as "6" or "7" indicating a positive interaction, but suggested aspects of the rating process itself could be improved; thus, the response is reflected in both the positive and negative columns here.[g]Four participants responded with both positive and negative comments, which were marked in both columns.[h]Two participants responded with both positive and negative comments, which were marked in both columns.[i]Another participant responding to question 6 indicated a fairly neutral response (i.e., there were aspects that the participant liked more about the web tool than a spreadsheet, and others they preferred about a spreadsheet); thus the response is counted in both the positive and negative columns here.[j]One participant responded with both positive and negative comments, which were marked in both columns.[k]Two participants responded with both positive and negative comments, which were marked in both columns.[l]N/A = not applicable.

protocols specifically designed to measure how much face-to-face discussion alters the outcomes of stakeholder judgments. Outcomes of such studies could help optimize the collection of web-based stakeholder input, which may become increasingly necessary given the reality of limited resources with which to engage large numbers of subject matter experts with diverse sector perspectives (e.g., industry, academia, non-governmental organizations).

In addition to providing a foundation for future investigations comparing face-to-face and web-based engagement methods, results of this work inform comparisons of web-based and other electronic engagement tools (e.g., spreadsheets). Expert stakeholders who participated in both processes could directly compare between CEAWeb and the spreadsheet tool (CEAPrioritize) that provided a foundation for the web-based tool. Participant feedback suggests that CEAWeb represents an overall improvement from a spreadsheet tool (5 generally positive responses, 3 generally negative responses; Table 1, Question 6). Based on some specific comments (e.g., "It is quite different from the other tools, & much preferred"), future applications of CEAWeb could not only reduce reliance on face-to-face interactions, but also facilitate increased participation compared to approaches using spreadsheets or other similar tools. Expert feedback on the pilot study for the CEAWeb will pave the way for more extensive use of a web-based process to enable the critical research planning and risk management needed to address ENMs and other emerging risks.

Future applications of CEAWeb with larger stakeholder groups can support the development of research plans for a variety of chemicals or materials that inform future risk assessments in a manner responsive to recent guidance (U.S. GAO, 2013). Information that emerges from future CEAWeb applications could be made publicly available via the internet and thus used to inform individuals developing research funding opportunities for ENM and other emerging materials throughout the scientific community (e.g., STAR grants, National Institutes of Health Request for Proposals). Indeed, a recent multi-stakeholder review of emerging methods for evaluating ENM highlighted the importance of using transparent, participatory approaches to move the application of such methods forward (Nel et al., 2013). The benefits and limitations of CEAWeb that we identified in this pilot study thus provide a critical foundation for applying web-based tools to meet the needs for stakeholder engagement in the field of ENM and other emerging areas.

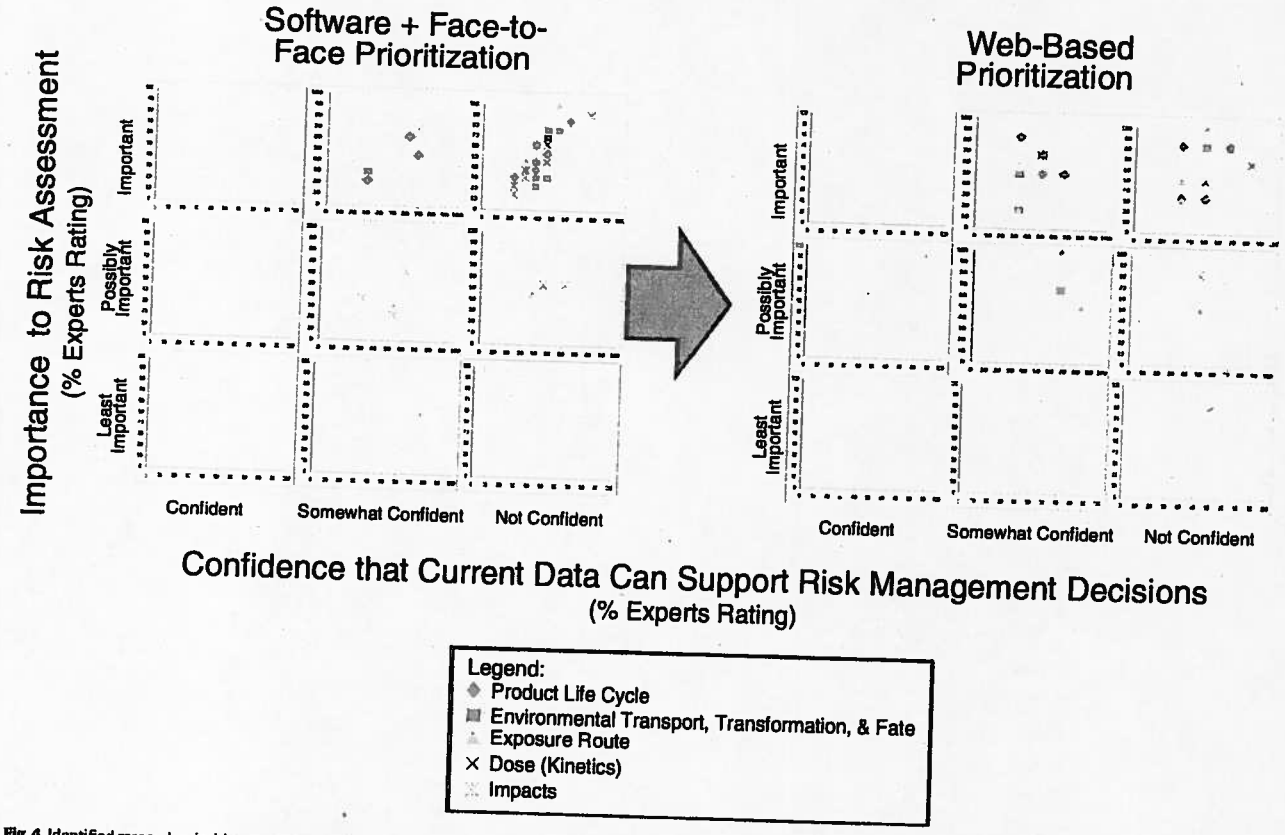

Fig. 4. Identified research priorities. Overview of research priorities identified through engaging stakeholders with a software tool combined with face-to-face discussion (left) compared to those identified in the CEAWeb pilot (right). Data are shown as percentage of participants. See Tables A.3 and A.4 for all data points.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.scitotenv.2013.10.016.

Disclaimer

Views expressed in this article are those of the authors and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency. The authors declare no competing interests.

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References

Abt E, Rodricks JV, Levy JI, Zeise L, Burke TA. Science and decisions: advancing risk assessment. Risk Anal 2010;30:1028–36.
Grieger KD, Linkov I, Hansen SF, Baun A. Environmental risk analysis for nanomaterials: review and evaluation of frameworks. Nanotoxicology 2012;6:196–212.
Jones R. Public engagement and nanotechnology the UK experience; 2009.
Linkov I, Seager TP. Coupling multi-criteria decision analysis, life-cycle assessment, and risk assessment for emerging threats. Environ Sci Tech 2011;45:5068–74.
Morgan K. Development of a preliminary framework for informing the risk analysis and risk management of nanoparticles. Risk Anal 2005;25:1621–35.
Nel AE, Nasser E, Godwin H, Avery D, Bahadori T, Bergeson L, et al. A multi-stakeholder perspective on the use of alternative test strategies for nanomaterial safety assessment. ACS Nano 2013;7(8):6422–33. http://dx.doi.org/10.1021/nn4037927.
NNI. Environmental health and safety research strategy. Washington, DC: National Science and Technology Council; 2011.
NRC. Public participation in environmental assessment and decision making. In: Dietz T, Stern PC, editors. Washington, DC: National Academies Press; 2008.
NRC. Sustainability and the U.S. EPA. Washington, DC: National Academies Press; 2011.
NRC. A research strategy for environmental, health, and safety aspects of engineered nanomaterials. Washington, DC: National Academies Press; 2012.
OECD. Important issues on risk assessment of manufactured nanomaterials. Series on the safety of manufactured nanomaterials, no. 33, Paris; 2012.
Powers CM, Dana G, Gillespie P, Gwinn MR, Hendren CO, Long TC, et al. Comprehensive environmental assessment: a meta-assessment approach. Environ Sci Tech 2012;46:9202–8.
RTI International. Nanomaterial case study workshop process: identifying and prioritizing research for multiwalled carbon nanotubes. Summary report—final. Research Triangle Park, NC: U.S. Environmental Protection Agency; 2012.
Tervonen T, Linkov I, Figueira JR, Steevens J, Chappell M, Merad M. Risk-based classification system of nanomaterials. J Nanopart Res 2009;11:757–66.
U.S. EPA. Nanomaterial case studies. Nanoscale titanium dioxide in water treatment and topical sunscreen (final), Research Triangle Park; 2010.
U.S. EPA. Nanomaterial case study. a comparison of multiwalled carbon nanotube and decabromodiphenyl ether flame-retardant coatings applied to upholstery textiles (draft), RTP, NC; 2012a.
U.S. EPA. Nanomaterial case study. Nanoscale silver in disinfectant spray (final report); 2012b [Washington, DC].
U.S. GAO. Chemical assessments. An agency wide strategy may help EPA address unmet needs for integrated risk information system assessments; 2013.
Wardak A, Gorman ME, Swami N, Deshpande S. Identification of risks in the life cycle of nanotechnology-based products. J Ind Ecol 2008;12:435–48.

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The Effects of Metals as Endocrine Disruptors

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THE EFFECTS OF METALS AS ENDOCRINE DISRUPTORS

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This review reports current knowledge regarding the roles that cadmium (Cd), mercury (Hg), arsenic (As), lead (PB), manganese (Mn), and zinc (Zn) play as endocrine-disrupting chemicals (EDCs). The influence of these metals on the endocrine system, possible mechanisms of action, and consequent health effects were correlated between experimental animals and humans. Analysis of the studies prompted us to identify some critical issues related to this area and showed the need for more rigorous and innovative studies. Consequently, it was recommended that future studies need to: (1) identify the mechanisms of action, because at the present time only a few have been elucidated—in this context, the possible presence of hormesis need to be determined, as currently this was reported only for exposure Cd and As; (2) study the possible additive, synergistic, or antagonistic effects on the endocrine system following exposure to a mixture of metals since there is a lack of these studies available, and in general or occupational environments, humans are simultaneously exposed to different classes of xenobiotics, including metals, but also to organic compounds that might also be EDCs; (3) assess the potential adverse effects on the endocrine system of low-level exposures to metals, as most of the information currently available on EDCs originates from studies in which exposure levels were particularly high; and (4) assess the effects on the endocrine and reproductive systems of other metals that are present in the general and occupational environment that have not yet been evaluated.

In 2002 the World Health Organization (WHO) defined endocrine-disrupting chemicals (EDCs) as "an exogenous substance or mixture that alters functions of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations." (WHO, 2002). Numerous chemical substances belong to this category, including persistent organic pollutants (POPs) such as dichlorodiphenyltrichloroethane (DDT) and its metabolites; industrial compounds such as dioxins, bisphenol A, and polychlorinated biphenyls (PCBs); pesticides such as chlorinated insecticides, imidazoles, and triazoles; chemical substances that are widely used in cosmetics, such as phthalates, ultraviolet (UV) filter constituents, and parabens; and also several heavy metals (Roy et al., 1997; Mantovani et al., 1999; Oishi, 2002; Tseng et al., 2003; Choi et al., 2004; Kunz & Fent, 2006). In recent years, increasing interest in this topic has led investigators to undertake numerous studies that yielded important information on the classification of EDCs, their mechanisms of action, and effects they have on the health of humans exposed to these xenobiotics (DeRosa et al., 1998).

Most studies performed on EDCs revealed that these substances act by means of a genomic mechanism of action, i.e., they act as hormone agonists for a specific receptor (Waring & Harris, 2005). However, the biological effects of these compounds cannot be wholly attributed to their interaction with hormone receptors, since studies also clearly indicated the presence of non-genomic mechanisms of action capable of altering, or at least influencing, the synthesis, transport, and availability of endogenous hormones (Waring & Harris, 2005). EDCs are therefore able to mimic endogen hormone activity and reproduce equivalent effects. EDCs also block natural hormone activity by a mechanism of action that competes for the receptors or can influence the physiological concentration of a hormone (Waring & Harris, 2005).

The endocrine system uses chemical messengers called hormones that are produced by specialized cells and released into the bloodstream. These secreted signaling molecules are chemically classified into water-soluble and lipid-soluble. Amine and peptide hormones bind to membrane receptors or cell-surface receptors, whereas steroids, as well as thyroid hormones, are small hydrophobic molecules that differ in chemical structure and function and that diffuse directly across cell

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plasma membranes and bind to intracellular receptors. These receptors are structurally related, constituting the nuclear receptor superfamily, and are activated after the binding of their specific ligands that include the glucocorticoid receptors (GRs), mineralocorticoid receptors (MRs), estrogen receptors (ERs), progesterone receptors (PRs), and androgen receptor (ARs). The regulation of gene expression by nuclear receptors is mediated through the subcellular distribution of inactive receptors, redistribution of activated receptors to nuclear domains, and direct interaction between nuclear receptors and co-factors (Ozawa, 2005; Katawa, 2008).

EDCs affect hormone systems by interfering mainly with steroid and thyroid hormones. Consequently the predominant effects on human health are alterations in the development and growth processes in exposed subjects (Mantovani, 2002), although a number of studies suggested that EDCs may also play an important role in the onset of cancer of the breast, ovaries, testicles, and prostrate (Donna et al.,1989; Keller-Byrne et al.,1997; Aronson et al., 2000; Weir et al., 2000; Band et al., 2002), and evidence indicated a possible involvement of EDCs in alterations in the immune (Ansar, 2000; Weisglas-Kuperus et al., 2004) and neurological systems (Tilson, 1998; Rodier, 2004; Wormley et al., 2004).

However, current knowledge of EDCs is still limited and considerable controversy surrounds this issue. There is disparity in the scientific community regarding assessment of the possible risk of exposure to EDCs since various investigators believe it to be disastrous, while others consider it to be uncertain or even insignificant (Colborn et al., 1996; Ames & Gold, 2000; Safe, 2000). Further studies are needed to investigate the levels of exposure to EDCs that may produce adverse effects on human health. Some studies demonstrated the existence of effects related to EDCs at low exposure doses, while other experiments that investigated the same EDC with identical models failed to obtain similar results (NTP, 2001). Another aspect that needs to be examined is the potential synergistic effect that may occur in the presence of exposure to a mixture of different EDCs with the same mechanism of action (Latini et al., 2003). Finally, most research into this subject has concentrated on a few groups of EDCs such as pesticides or POP, whereas information on a number of other xenobiotics that may act as EDCs is still scant and incomplete. In this review current knowledge regarding the role that some metals play as EDCs was assessed, including analysis of mechanisms of action, influence on the endocrine system, and consequent health effects observed due to exposure to these metals. The aim of this analysis was to identify research areas in this particular EDC category where further study needs to be carried out in order to attain a greater understanding of the issue.

CADMIUM

Cadmium (Cd) is a heavy metal widely found in a number of environmental matrices. Elevated concentrations of this metal in soil and reservoirs are the result of heavy emissions from different sources of pollution (Jarup et al., 1998; Bhattacharyya et al., 2000). The extraction, foundry, metallurgical, and electroplating industries are the main sources of occupational exposure to Cd, while exposure in the general population occurs through the ingestion of contaminated foods (meat, fish, fruit) or contact with consumer products containing this metal (nickel/cadmium batteries, pigments, paints, plastic products) (Jarup et al., 1998; Zadorozhnaja et al., 2000). Cadmium exposure is linked to numerous human health problems, including an increased incidence of renal pathologies, osteoporosis, leukemia, and hypertension, and is involved in the onset of lung cancer (Satoh et al., 2002). In 1993, the International Agency for Research on Cancer (IARC) included this metal and its compounds in Group 1, thereby classifying it as carcinogenic to humans (IARC, 1993).

Various studies demonstrated the effects of this metal on hormones. Plasma concentrations of gonadotropins, prolactin, adrenocorticotropic hormone (ACTH), growth hormone (GH), and thyroid-stimulating hormone (TSH) were measured in adult Sprague-Dawley rats exposed to cadmium chloride ($CdCl_2$) in drinking water at doses of 5, 10, 25, 50, or 100 ppm for 1 mo. Lafuente et al. (2003) showed that Cd differentially affected the secretory patterns of pituitary hormones such as gonadotropin, prolactin, ACTH, GH, and TSH. In fact, the lower dose of Cd increased plasma prolactin levels and higher doses (25 or 50 ppm) decreased hormone levels. There was a continuous

increase of plasma ACTH levels at the low to 25 ppm dose but a decrease returning to basal values with the highest dose. Plasma GH levels increased with a dose of 10 ppm, but doses of 5, 25, and 50 ppm decreased these levels. Plasma luteinizing hormone (LH) levels fell only with a dose of 50 ppm, whereas follicle-stimulating hormone (FSH) levels rose. Doses of 5, 25, and 100 ppm increased plasma TSH levels. The effects of Cd on prolactin and ACTH were dose dependent (Lafuente et al., 2003).

The subcutaneous (sc) injection (0, 3, or 5 mg/kg) of Cd on the day of diestrus and on the d 7 and 16 of gestation in Sprague-Dawley rats produced an inhibition of progesterone synthesis (Piasek & Laskey, 1994). A similar result was obtained in vitro on human ovarian granulosa cells obtained from 41 women undergoing ovulation induction and ovum retrieval for the purpose of in vitro fertilization (Paksy et al., 1997). Cells were treated with 8, 16, 32, and 64 μM of $CdCl_2$ for 2, 4, 8, 24, or 48 h. Progesterone production by granulosa cells was decreased by Cd during the 48-h exposure period and the response was marked and concentration dependent, attaining significance at 16 μM.

A reduction of progesterone production was also observed in cells obtained from ovaries of Sprague-Dawley rats killed on the day of proestrus, or on gestation day 6 or 16 (Piasek & Laskey, 1999). Culture from each ovary was incubated with $CdCl_2$ at concentrations of 0, 100, 500, 1000, 1500, or 2000 μM. The 1-h whole-ovary production of progesterone, testosterone, and estradiol was determined and results showed that in proestrus rats, and to a lesser extent in pregnant dams, production of progesterone and testosterone was most affected, whereas estradiol was not affected. Thus, data suggest that Cd may interfere directly with hormone production in steroid-production ovary cells.

Some studies conducted on human trophoblast cells noted that Cd exerted an inhibitory effect on progesterone placental synthesis. In fact, Jolibois et al. (1999a) observed that after 72 h of continuous exposure to Cd at concentrations of 5, 10, or 20 μM, progesterone release was significantly reduced to 69, 51, and 38% of control values, respectively. When cells were exposed to metal from 72 to 96 h, progesterone release exhibited the same pattern of decline in response to increasing Cd concentrations. In another study conducted under the same experimental conditions Joblibios et al. (1999b) investigated potential mechanisms by which Cd inhibits progesterone release and found that transcription of the low-density lipoprotein receptor LDL-R mRNA may be inhibited by Cd exposure because the abundance of LDL-R mRNA in trophoblast cells fell in a concentration-dependent fashion in vitro, potentially resulting in reduced cholesterol substrate available for placental progesterone production.

A similar study was conducted on human cytotrophoblasts obtained from 18 human placentas at term of uncomplicated pregnancies (Kawai et al., 2002). Cells were incubated with 0, 5, 10, or 20 μM of $CdCl_2$ for 96 h. Data demonstrated that enzyme P-450 cholesterol side-chain cleavage is one site at which the metal interferes with progesterone production in cultured human trophoblasts. Although these studies conducted on human trophoblasts indicate that this metal exerts an inhibitory effect on placental progesterone synthesis (Jolibois et al., 1999a, 1999b; Kawai et al., 2002), not all data in the literature confirm these findings. In fact, a number of in vivo and in vitro studies reported an increase in serum progesterone levels and in synthesis of this hormone in laboratory animals and in cell cultures exposed to Cd^{2+}. Powlin et al. (1997) observed that progesterone and human chorionic gonadotropin (hCG) syntheses are increased in JAr choriocarcinoma cells, a neoplastic trophoblast cell line that is similar to early human trophoblast, treated with 20 and 40 μM Cd as $CdCl_2$ for 24 h. Furthermore, Massányi et al. (2000) found that Cd as $CdCl_2$ induced an increase in progesterone production and a decrease in 17-β-estradiol production in ovarian granulosa cells at concentrations of 0.2, 10 and 20 ng/ml for 48 h.

The effects of Cd^{2+} on progesterone synthesis have also been investigated using a stable porcine granulosa cell line (JC-410). Smida et al. (2004) showed that low and elevated $CdCl_2$ concentrations exert opposite effects on progesterone synthesis with a biphasic dose response. After 48-h incubation, $CdCl_2$ at 1, 2, or 3 μM inhibited hormone synthesis to 0.48-, 0.38-, and 0.29-fold respectively, while there was stimulation in production by 1.6-fold at 0.1 μM.

It was shown that exposure to Cd^{2+} during gestation is associated with reduced birth weight of newborn and an increase in the number of spontaneous abortions and preterm births. Nishijo et al. (2002) observed that the rate of preterm deliveries of mothers with higher urinary Cd (≥2 nmol/mmol creatinine) was greater than that of mothers with lower urinary Cd (≤2 nmol/mmol creatinine). The height and weight of newborn infants of mothers with higher urinary Cd were significantly lower than those of the newborn infants of mothers with lower urinary Cd, but these decreases were ascribed to early delivery induced by Cd. Similar results were observed also in a study conducted on 102 mothers and their newborns to investigate the effect of low levels of Cd on birth weight (Frery et al., 1993). The main finding of this study was the relationship between a decrease in birth weight and an increase in newborn hair Cd, which varied in the presence of placental calcification. In the presence of calcification, an increase in the level of Cd (0.11 ppm) in newborn hair was related to a decrease in birth weight that was independent of placental Cd concentration (11.8 ng/g), while in the absence of calcification, a decrease in birth weight was observed only for the upper values of newborn hair Cd (0.145 ppm). A possible explanation for these effects may be due to the influence of Cd on synthesis of some hormones such as hCG that play a vital role in the maintenance and progression of pregnancy. In fact, using a human placental perfusion model, Wier et al. (1990) demonstrated that exposure to 20 and 100 nmol/ml $CdCl_2$ inhibited the production of hCG.

Finally, Garcia-Morales et al. (1994) showed that Cd^{2+} exerts an estrogenic effect both in vivo and in vitro. In the human breast cancer MCF-7 cell line, Cd mimicked estrogen action, inducing after 24 h at a concentration of 1 μM a reduction of 58% in gene transcription for the estrogen receptor (ER) and increasing 5.6-fold gene expression for the progesterone receptor (PR). Cd also posseses potent estrogen-like activity in vivo. In fact, treatment of female Sprague-Dawley rats with a single intraperitoneal (ip) injection at a dose of 5 μg/kg $CdCl_2$ resulted in increased uterine wet weight, promoted growth and development of the mammary glands, and induced hormone-regulated genes in ovariectomized animals. Furthermore, female offspring experienced an earlier onset of puberty (Johnson et al., 2003).

The development of the germ cells and fetal gonads during the prenatal period and of postnatal gonadal maturation and fertility was studied by Tam and Liu (1985) in ICR mouse embryos and in offspring of female ICR mice treated with $CdCl_2$. Pregnant mice were given an ip injection of metal (5–6 mg/kg body weight) at 7.5 or 8.5 d. Results of this study revealed that mouse embryos treated with Cd during organogenesis had a reduced germ cell population and showed poor gonadal development. Moreover, males from Cd-treated litters displayed poor mating performance and a higher incidence of sterile matings. The testes were smaller as a result of poor gonadal growth in the prenatal and postnatal period, and the subfertility of the male offspring is the consequence of lack of germ cells, poor gonadal development, and abnormal production of spermatozoa. Gonadal damage was also observed in adult male rats following oral and sc administration of Cd (Kotsonis & Klaassen, 1977). In this study the single oral administration of 100–150 mg Cd/kg produced focal testicular necrosis and reduced spermatogenesis in treated rats, while sc injection of 7 mg/kg of $CdCl_2$ produced significant testicular hemorrhage and edema 24 h after treatment.

Leoni et al. (2002) studied the effects of three different concentrations of $CdCl_2$ (0, 2, or 20 μM) on acrosome integrity and sperm viability in sheep. Data showed that spermatozoa exposure to Cd decreased sperm viability and increased sperm acrosome reaction. In particular, the high concentration of metal (20 μM) produced lethal effects on sperm, decreasing the viability of spermatozoa to 35.6% when compared with control viability of 54.4%. Decreased cell viability may be due to an increase in reactive oxygen species (ROS) and a decrease in cell antioxidant defense systems including catalase (CAT), glutathione (GSH), and GSH peroxidase. The low concentration of Cd (2 μM) induced a significant modification of acrosome membrane integrity compared to control and high-concentration groups. The maintenance of the acrosome is essential to the functional integrity of sperm for binding to the zona pellucida and for response to the appropriate signals of oocytes.

MERCURY

Mercury (Hg) is a metal that is widely used in foundry, mining, and manufacturing industries and is a component in a number of electrical instruments and medical products (thermometers, thermostats, dental amalgams, switches, batteries) (Gochfeld, 2003). Occupational exposure occurs mainly among chloro-soda factory workers and those engaged in the manufacture of precision instruments, Hg vapor lamps, new compact fluorescent bulbs, and batteries (Gochfeld, 2003). The general population is exposed to Hg principally via the ingestion of contaminated foods in particular fish where Hg accumulates in the form of methylmercury (MeHg) (Bayen et al., 2005; Bhan & Sarkar, 2005). Mercury exposure also occurs in the general population through dental amalgams that release this metal during mastication (Ratcliffe et al., 1996; Gochfeld, 2003). Clinically, acute Hg poisoning, which is a rare and usually accidental occurrence, manifests itself as chemical pneumonia, while prolonged exposure results in the onset of tremors, erethism, and stomatogingivitis (Bhan & Sarkar, 2005). In addition, a threshold for Hg-induced immunotoxicological effects is likely, and multiple exposure scenarios involving high or chronic exposures leading to increased body burden are linked to enhanced risk of immunomodulation (Sweet & Zelikoff, 2001).

Some studies postulated that Hg may influence physiological levels of reproductive hormones (Agusa et al., 2007). In fish oocytes (*Channa punctatus*), exposed to 115 µg/L of mercuric chloride ($HgCl_2$) (short-term 2-d exposure) and 23 µg/: $HgCl_2$ (chronic exposure for 35 d), a significant induction of the expression of 3-beta-hydroxy-delta-5-steroid dehydrogenase and an increase in progesterone synthesis were noted (Mondal et al., 1997). The administration of MeHg at doses of 0.06 (control), 0.87 (low exposure), and 3.93 (medium exposure) µg/g dry weight in the diet of male and female fathead minnows (*Pimephaleas promelas*) lowered testosterone and 17β–estradiol plasma levels. In fact, male fish fed the control diet had mean testosterone concentrations 20% and 106% greater than those fed the low and medium diets, while control females had mean estradiol concentration 149% and 402% greater than those fed the low and medium diets (Drevnick & Sandheinrich, 2003). The ip injection of MeHg (5 and 10 µg/kg) and $HgCl_2$ (50 and 100 µg/kg) in male albino rats for 90 d led to a gradual reduction in 3β-hydroxy-Δ^5-steroid dehydrogenase activity in Leydig cells, and produced a significant decrease in serum testosterone levels (Vachhrajani & Chowdhury, 1990). The adverse action of Hg on cells that produce steroid hormones was also revealed by administering 10 or 100 µ*M* $HgCl_2$ to Leydig and adrenal cells isolated from testicles and adrenal glands of male Sprague-Dawley rats. Treatment with Hg produced a reduction in the production of corticosterone and testosterone (Ng & Liu, 1990).

Mercury also interferes with the process of spermatogenesis. In male albino rats, ip administration of $MeHgCl_2$ (0, 5, and 10 µg/kg) or $HgCl_2$ (0, 50, and 100 µg/kg) resulted in a reduction in sperm motility and sperm count (Chowdhury et al., 1989). A study conducted on female Sprague-Dawley rats exposed to 0, 1, 2, or 4 mg/m^3 elemental Hg vapor demonstrated that estrus cycles were prolonged in the 2- and 4-mg/m^3 dose groups. Furthermore, in rats exposed to 4 mg/m^3 elemental Hg vapor, serum estradiol was significantly decreased compared to control and progesterone was significantly increased. Davis et al. (2001) concluded that exposure to Hg brings about an alteration in the estrus cycle but does not affect ovulation, implantation, and maintenance of pregnancy. Nonetheless, there is a disparity among the data available since the administration of Hg to laboratory animals has often resulted in notable problems related to reproductive toxicity such as spontaneous abortions, congenital malformations, infertility, and inhibition of ovulation (Schuurs, 1999). In fact, Berlin et al. (1992) reported a dose-related incidence of abortion, neonatal mortality, and a decrease in birth weight in squirrel monkeys exposed to 1000 µg Hg^0/m^3 air for daily periods of different duration. The exposure began at wk 3–7 of gestation and continued to the termination of pregnancy.

A number of studies reported an association between Hg exposure in humans and serum hormone levels. Results of a study conducted on 20 subjects (5 males and 15 females) from Cambodia with Hg concentrations in the hair and blood of 0.69–190 µg/g dry weight and 5.2–58 µg/L, respectively, indicated that serum estrone and estradiol levels were positively correlated with blood Hg levels for both males and females, indicating possible induction of female hormones by Hg exposure (Agusa et al., 2007).

Occupational exposure (10 yr on average) to Hg vapor in 41 chloroalkali workers with a mean urinary Hg concentration of 15 nmol/mmol creatinine and a mean blood Hg concentration of 46 nmol/L was associated with an increase in both serum free thyroxine (T4) concentration and the T4/triiodothyronine (T3) ratio, and a decrease in serum free T3 levels (Baaregard et al., 1994). Data suggested that Hg may interfere with thyroid metabolism by negatively influencing type I iodothyronine deiodinase that catalyses activation of the thyroid T4 to its active T3 form. A similar study performed on the same category of 47 workers in Norway confirmed this result (Ellingsen et al., 2000). Workers exposed to Hg vapor for an average of 13.3 yr were compared with 47 referents matched for age in a cross-sectional study of thyroid function. The mean urinary Hg concentration in the exposed workers was 5.9 nmol $mmol^{-1}$ creatinine (range 1.1–16.8) versus 1.3 nmol $mmol^{-1}$ creatinine (range 0.2–5) reference group. The median serum concentration of reverse triiodothyronine (rT3) was statistically significantly higher in exposed compared to referent subjects. The free T4/free T3 ratio was also higher in the highest exposed subgroups compared with referents. Finally, a positive association between Hg exposure and serum TSH concentration was reported in a study conducted on 259 subjects from two regions of Quebec (Canada) (Abdelouahab et al., 2008).

ARSENIC

The use of arsenic (As) in (1) agricultural products such as herbicides and fungicides, (2) the foundry industry, and (3) combustion of fossil fuels is a predominant source of environmental As pollution (Vahidnia et al., 2007). Exposure of the general population occurs mainly through the ingestion of contaminated food and water, while occupational exposure to As occurs in workers in the paint, ceramics, pesticide, insecticide, and wood preservatives industries (Ratnaike, 2003). Acute poisoning produces nausea, vomiting, diarrhea, psychosis, peripheral neuropathy, and skin rash (Ratnaike, 2003). Chronic exposure to this metal results in the onset of organ and system symptoms such as hyperpigmentation and keratosis palmaris, recurring bouts of diarrhea, vomiting, arrhythmia, hypertension, and peripheral sensitive neuropathy (Ratnaike, 2003). In addition, exposure to As is associated with the onset of cancer of the skin, lungs, kidneys, liver, and bladder (Bernstam & Nriagu, 2000; Tsai et al., 1998).The IARC included this metal in Group 1, i.e., among substances that are carcinogenic in humans (IARC, 1998).

Moreover, results from animal studies demonstrate that As produced developmental toxicity, including malformation, death, and growth retardation. Golub et al. (1998) suggested that environmental As exposures are primarily a risk to the developing fetus.

In recent years, numerous studies have been performed to understand the mechanisms of action responsible for the effects of As on human health. Great importance has been given to the role of metal speciation in endocrine disruption and to their relationship with some classes of hormone receptors. The results of these studies suggest that many As-related adverse human health effects are due to the way this metal influences the endocrine system (Watson & Yager, 2007). In a study conducted on H4IIE rat hepatoma cells, the administration of non-cytotoxic doses (0.3–3.3 μM) of sodium arsenite ($NaAsO_2$) produced an inhibition of nuclear transcription activity of the glucocorticoid receptor (GR) (Kaltreider et al., 2001). Evidence indicated that inhibition occurred at a nuclear level and did not depend on a mechanism by which the metal competes for the ligand binding site of the receptor (Kaltreider et al., 2001). Bodwell et al. (2004) reported that 0.05–1 μM (6–120 ppb) As exerted stimulatory effects on GR-mediated gene activation in rat EDR3 hepatoma cells of both the endogenous tyrosine aminotransferase (TAT) gene and the reporter genes containing TAT glucocorticoid response elements. At higher concentrations (1–3 μM), the effects of As became inhibitory. Thus, over this narrow concentration range, the effects of As changed from a two- to fourfold stimulation to a greater than twofold suppression in activity. In the same cell line, with As concentrations ranging from 0.045 to 2.7 μM, a similar biphasic response was also observed for the mineralcorticoid receptor (MR), androgen receptor (AR), and PR (Bodwell et al., 2006). Findings from this study therefore suggest that As inhibits or activates responses, but the mechanism of action probably remains the same.

The effects of As exposure on ER were investigated with the human breast cancer MCF-7 cell line. Treatment of cells with non-cytotoxic levels of As (0.25–3 μ*M*) resulted in a significant inhibition of estradiol-mediated genomic activation, while no stimulatory effect was observed at low exposure levels (Davey et al., 2007). Similar results were also obtained in an in vivo study with administration of non-cytotoxic concentrations (1–50 μ*M*/kg) of $NaAsO_2$ to chicken embryos, where Davey et al. (2007) showed a significant inhibition of ER-dependent gene transcription of the 17β-estradiol (E2)-inducible vitellogenin II gene. Arsenic also exerts effects similar to those reported for steroid receptors in gene regulation mediated by the retinoic acid receptor (RAR) and by the thyroid hormone receptor (TR). In fact, administration of sodium arsenite (0.01–5 μ*M*) in the NT2 human embryonic carcinoma cells and in the GH3 rat pituitary tumor cells revealed a biphasic response, similar to the one observed for steroid receptors, on genomic-mediated induction by RAR and TR (Davey et al., 2008).

The effects of this metal on the male reproductive system have not yet been fully elucidated, although there are a number of in vivo studies that reported sperm toxicity, inhibition of testicular androgenesis, and reduction in testicular and accessory sex organ weights. Sarkar et al. (2003) administered ip to male Wistar rats sodium arsenite at doses of 4, 5, or 6 mg/kg for 26 d to evaluate these effects. In the 5- and 6-mg/kg groups, there were significant dose-dependent decreases in the accessory sex organ weights, epididymal sperm count, and plasma concentrations of LH, FSH, and testosterone. The changes were significant at 5 or 6 mg/kg group. In another study, the administration of sodium arsenite (4 mg/kg) for 365 d in the drinking water of mice (*Mus musculus*) produced a significant reduction in testicular weight, sperm count and motility, and testicular enzymatic activities (Pant et al., 2004). Similar results were obtained in a study in which male Sprague Dawley rats were administered 5 mg/kg sodium arsenite in drinking water for 6 d/wk for 4 wk. Findings revealed an alteration in the reproductive functions of treated animals with a reduction in testicular mass and decrease in plasma concentrations of testosterone and gonadotropin (Jana et al., 2006). After reporting similar spermatogenic degeneration in animals treated with estradiol, Jana et al. (2006) suggested that an estrogen-type mechanism of action may be responsible for As-related reproductive toxicity. This postulation was confirmed by Stoica et al. (2000) in a study conducted on human breast cancer cell line MCF-7 treated with 0.1, 1, 5, or 10 μ*M* of sodium arsenite. In fact, similar to estradiol, arsenite decreased the expression of ERα and increased the expression of the progesterone receptor. Moreover, the estrogen-like effects of arsenite were inhibited by an antiestrogen, suggesting that these responses were mediated by ERα. A marked effect noted was the ability of arsenite to activate ERα at concentrations as low as 1 n*M*. Thus As appears to activate ERα through the formation of a high-affinity complex with the hormone-binding domain of the receptor, which blocks the binding of estradiol. Finally, it was shown that As exposure in utero resulted in marked alterations in gene expression in fetal liver involving a complex interplay between steroid metabolism and estrogen signaling pathways (Liu et al., 2007). In fact, oral administration of sodium arsenite (85 mg/kg in drinking water) to pregnant C3H mice from d 8 to d 18 of gestation resulted in an overexpression of various estrogen-linked genes (such as Xist, Agr2, Tffl, CRP-ductin, Ghrl, Krt1-19, and Cyp2a4). Alterations in the expression of these genes are reflective of endocrine disruption effects of inorganic As at an early life stage.

LEAD

Most of the lead (Pb) that is present in environmental matrices originates from anthropogenic sources. Lead is used in the production of batteries, cables, pigments, and chemical additives and was employed in petrol products (WHO, 1995). The main sources of environmental Pb pollution are from foundry and mining industries, refineries, waste disposal, and Pb-recycling industries (WHO, 1995). In countries where leaded petrol is still in use, motor vehicle traffic constitutes the main source of air pollution due to Pb emissions (WHO, 1995). The general population is exposed to Pb via the ingestion of contaminated food and water and inhalation of airborne Pb (WHO, 1995). Lead exposure produces a wide range of adverse effects on human health, effects such as anemia, psychological disorders, peripheral neuropathy, nephropathy, and abdominal colic (WHO,

1995). Blood Pb levels ranging from 5 to 10 μg/dl were associated with neurobehavioral disorders and a significant reduction in cognitive capacity in children due to impaired levels of attention, concentration, and memory (Téllez-Rojo et al., 2006; Surkan et al., 2007, Counter et al., 2009). Furthermore, effects on the female reproductive system (alterations in pregnancy) and male reproductive system (morphological alterations in spermatozoa and the sperm count) have also been linked to Pb exposure (WHO, 1995).

One of the main causes of Pb-related reproductive toxicity stems from the way this metal affects the endocrine system. In fact, there are numerous studies in the literature concerning the relationship between Pb exposure and physiological activity of hormones. In virgin albino NMRI mice, intravenous (iv) injection of 75 ppm Pb chloride, giving blood levels of about 32 μmol/L, produced a significant reduction in embryo implantations compared to the control. Serum 17β-estradiol and progesterone levels were similar in exposure and controls, suggesting that the effects of the metal are linked to altered activity of uterine estrogen receptors and their affinity for ovarian steroids (Wide, 1980). Based upon these results, exposure to Pb seems not to pose a risk with respect to progesterone secretion. In fact, a study conducted on cultured granulosa cells obtained from follicular aspirates of six patients undergoing in vitro fertilization and embryo transfer confirmed these data (Paksy et al., 2001). Human granulosa cells were cultured for 48 h in the presence of different concentrations of Pb acetate (100, 200, 400, 800, or 1600 μ*M*), and only exposure to the highest concentration resulted in a significant decrease in progesterone production. Ovarian toxicity of Pb was investigated also in 40 adult virgin Swiss Albino female mice (Junaid et al., 1997). Animals were divided into 4 groups of 10 mice each and were given Pb acetate in deionized water through gavage for 60 d in 3 doses of either 2, 4, or 8 mg/kg/d. Data showed that Pb seems to affect follicular development and maturation at sufficiently high concentrations. In particular, small and medium follicles were significantly affected even at the lowest dose (2 mg), while large follicles were affected mostly at the highest dose (8 mg).

In female Sprague-Dawley rats that had been given drinking water containing 20 or 200 ppm concentrations of Pb chloride, prenatal and/or postnatal exposure to the metal resulted in an alteration in the number and affinity of uterine estrogen receptors both in adult and prepubertal rats (Wiebe & Barr, 1988). Similar alterations were also reported in LH ovary receptors. In fact, in the female offspring of Sprague-Dawley rats exposed during pregnancy to 20- or 200-ppm doses of Pb chloride, Wiebe et al. (1988) reported alterations in binding between gonadotropins and their respective ovary receptors, accompanied by a change in steroid production. Changes in hormone secretion were also demonstrated in an experiment in which a 12-mg/ml concentration of Pb acetate was administered to female Fischer 344 (F344) rats in drinking water during pregnancy and lactation. Findings from this study revealed that puberty was retarded in the offspring of treated animals and there was a noticeable reduction in plasma levels of insulin-like growth factor (IGF-1), LH, and estradiol (Dearth et al., 2002). Similar results were observed in a dose-response study conducted in a rat model where beginning on gestational day 5, time-impregnated female Sprague Dawley rats were given ad libitum access to either 0.05, 0.15, or 0.45% (w/v) Pb acetate until weaning, and thereafter pups received Pb acetate until euthanization (Ronis et al., 1998b). A significant dose-responsive decrease in birth weight was observed in all Pb-exposed litters and a delay in sexual maturity was measured by prostate weight in male pups and time of vaginal opening in female pups. Data from this study demonstrated that Pb produces a significant and dose-related suppression of normal sex steroid surges observed at birth and during puberty. In fact, in male pups there was a suppression of plasma concentrations of testosterone accompanied by a significant decrease in plasma LH, elevated pituitary LH content, and a decrease in plasma testosterone/LH ratios at the highest dose, while in female pups they observed a suppression of the plasma concentrations of estradiol during puberty. The mechanism of action responsible for inhibition of estradiol synthesis was studied in the female offspring of F344 rats treated with 12 mg/ml Pb acetate. Srivastava et al. (2004) reported a reduction of the expression of the steroidogenic acute regulatory protein (StAR) gene in the ovaries of these animals and a concomitant increase in estradiol synthesis. The administration of pregnant mare serum gonadotropin (PMSG) restored normal StAR expression and consequently the production of estradiol, indicating that the metal does not exert a direct effect

on ovary response to gonadotropins, but might act on the hypothalamus–hypophysis axis, altering LH release needed for both StAR and estradiol synthesis (Srivastava et al., 2004). The expression of StAR protein was studied also in vitro using the MA-10 mouse Leydig tumor cell line exposed to Pb acetate concentrations ranging from 10^{-8} to 10^{-5} *M* (Huang et al., 2002). Data suggested that the inhibitory mechanisms of Pb at the sites along signal transductional and steroidogenic pathways in MA-10 cells are dependent upon factors such as incubation time and concentration. In fact, the 3-h Pb incubation resulted in higher decreases in expression of StAR protein, human chorionic gonadotropin-stimulated progesterone production, and the activity of 3β-hydroxysteroid dehydrogenase compared to 2 h incubation. Surprisingly, Pb at 3 h of incubation did not affect P-450 side-chain cleavage enzyme activity, while this enzymatic activity was inhibited by the metal at 2 h.

The relationship between Pb exposure, gonadotropin secretion, and sexual hormones was also studied in female Sprague-Dawley rats that were administered Pb acetate (0.6% w/v) in prepuberty (group 1), postpuberty (group 2), and during pregnancy (group 3) (Ronis et al., 1996). In male offspring from group 1, the weight of secondary sex organs was significantly lower than controls, and serum testosterone levels were considerably reduced, especially in the offspring of group 3. Moreover, Pb affected LH secretion, causing it to vary in relation to the age at which Pb exposure occurred. This prompted Ronis et al. (1996) to suggest that Pb affected the hypothalamus–pituitary–gonadal axis at multiple action sites. In regard to the possible inhibitory effect of Pb on GH secretion proposed by Huseman et al. (1992), Ronis et al. (1996) found that alterations in the pubertal growth of male offspring were due to delayed development of the GH hormone system. There was a significant inhibition of estradiol levels in the female offspring of animals treated during pregnancy, while in the female offspring of animals treated prior to puberty, vaginal opening was delayed along with alterations in the menstrual cycle (Ronis et al., 1996). Similar data were reported for female Swiss rats in which plasma Pb concentrations of 13.2 µg/dl resulted in the delayed onset of puberty by approximately 7 d, while, surprisingly, plasma Pb concentrations ranging from 0.7 to 3 µg/dl prompted an earlier onset of puberty by approximately 12 d (Iavicoli et al., 2004). This finding was confirmed by Iavicoli et al. (2006) in a study conducted on the second- and third-generation offspring of animals treated as in the previous experiment. The effect of Pb on vaginal opening and estrus cycling was studied also by Ronis et al. (1998a) in a study where reproductive, endocrine, and growth effects of developmental Pb exposure were assessed using a rat model in which 0.6% Pb acetate (w/v) was administered in the drinking water ad libitum. Sprague-Dawley rats were divided in 5 groups with exposure to Pb from gestational day 5 through birth (group 1), during pregnancy and lactation (group 2), during lactation only (group 3), from birth through adulthood (group 4), and from gestational day 5 through adulthood (group 5). The results of this study showed that a significantly delayed vaginal opening and disrupted estrus cycling were observed in female pups of group 4 and group 5. In addition, continuous Pb exposure lowered serum testosterone levels in adult male offspring. Moreover, Pb exposure decreased birth weight in all animals exposed in utero and mean body weights were significantly lower in all Pb-treated groups up to weaning.

A number of studies correlated Pb exposure with modifications in the reproductive system. Sokol and Berman (1991) demonstrated that Pb acetate produced male reproductive toxicity, in particular after puberty. Male Wistar rats aged 42 d, 52 d, and 70 d were given Pb acetate (at 2 different doses of 0.1 or 0.3%) in drinking water for 30 d prior to sacrifice. Serum testosterone and sperm concentrations and production rate were significantly reduced in those animals that were exposed to Pb acetate starting at age 52 d and 70 d, but not 42 d. Kempinas et al. (1994) evaluated the effects of Pb on the male reproductive system in pubertal Wistar rats treated with 1 g/L lead acetate in drinking water for 20 d (subacute group) or 9 mo (8 chronic group) in addition to iv injections of Pb acetate (0.1 mg/100 g body weight) every 10 (subacute group) or 15 d (chronic group). Basal levels of testosterone were higher both in plasma and testes of acutely intoxicated animals while circulating levels of LH were not affected in either group; nor was the LH-releasing hormone content of the median eminence. Hsu et al. (1998) investigated the effect of Pb toxicity on sperm functions in male Sprague Dawley rats that received weekly ip injections of 20 or 50 mg Pb acetate/kg for 6 wk. Data demonstrated that reactive oxygen species (ROS) mediated toxicity of Pb on spermatozoa

by accelerating capacitation and acrosome reaction. Moreover, the observed decrease in the penetration of the zona-intact oocytes might be explained by Pb-induced ROS-related early onset of capacitation and premature acrosome reaction. These might affect the capability of spermatozoa to become incorporated into the plasma of oocytes and then probably affect fertilization. Wadi and Ahmad (1999) studied Pb toxicity in the male reproductive system, treating sexually mature male CF-1 mice with 0.25 or 0.5% Pb acetate in drinking water for 6 wk. Low-dose Pb significantly reduced the number of sperm within the epididymis, while the high dose reduced the sperm count and percent motile sperm, increased percent abnormal sperm within the epididymis, and decreased the epididymis and vesicular weights as well as overall body weight gain.

A number of studies reported various abnormalities in the reproductive system in men exposed to Pb. Gennart et al. (1992) observed in workers of a battery factory that a mean duration of exposure of 10.7 yr to Pb produced asthenospermia and oligospermia or terratospermia if blood Pb level was 61 μg/dl or between 41 and 75 μg/dl, respectively. A cross-sectional survey of the semen of 503 men employed by 10 companies was conducted in the United Kingdom, Italy, and Belgium. The median sperm concentration was reduced by 49% in men with blood Pb levels above 50 μg/dl (Bonde et al., 2002). Recently, Kapserczyk et al. (2008) reported that high exposure to Pb produced a decrease of sperm motility in men, most likely as a result of increased lipid peroxidation in seminal plasma, represented as malondialdehyde (MDA) levels, especially if blood Pb levels exceeded 40 μg/dl.

OTHER METALS

Although most studies performed to assess the role of metals as EDCs focused on Cd, Hg, As, and Pb, in recent years investigators turned their attention to other metals, especially manganese (Mn) and zinc (Zn), to study effects these metals may exert on the endocrine system.

Manganese

There are inorganic and organic Mn compounds, with the inorganic forms being the most common in the environment (Santamaria, 2008). Uses of Mn include iron and steel production, the manufacture of dry-cell batteries, and the production of potassium permanganate. Other Mn chemicals are used as oxidants in production of hydroquinone, manufacture of glass, textile bleaching, as oxidizing agent for electrode coating in welding rods, in matches and fireworks, and in the tanning of leather (Saric, 1986). Mn produces neurotoxicity, and its toxicity has been observed primarily in occupational environments such as Mn mining and smelting, battery manufacturing, and steel production (Santamaria et al., 2007). John Couper (1837) was the first to report neurological effects associated with exposure to Mn when he described muscle weakness, limb tremor, whispering speech, salivation, and a bent posture in five men working in a Mn ore crushing plant in France. This collection of symptoms was called "manganism" and it is a neurological syndrome that resembles Parkinson's disease, but there is considerable evidence that Mn preferentially damages different areas of the brain from those that are affected in Parkinson's disease (Calne et al., 1994; Olanow, 2004).

Animal studies demonstrated that exposure to Mn may affect the normal function of the endocrine system, in particular altering the production and secretion of sexual hormones (Pine et al., 2005). In female Sprague-Dawley rats, the administration of a range of concentrations (1, 2.5, 5, 10, or 25 μg/3 μl) of manganese chloride ($MnCl_2$) in the third ventricle of the brain stimulated LH release in a significant and dose-dependent manner, demonstrating that this metal affected gonadotropin secretion in the hypothalamus. In the same study, a second group of animals underwent (by gavage) exposure to 10 mg/kg of $MnCl_2$ for a period of 18 d. This second experiment resulted in the early onset of puberty (Pine et al., 2005). Pine et al. (2005) conducted a further study to ascertain whether the effects observed in females could be replicated in male Sprague-Dawley rats and showed that there was a positive influence on LH release from the hypothalamus and secretion of the luteinizing-hormone releasing hormone (LHRH) from the medial basal hypothalamus. Moreover, in rats that were administered a dose of 25 mg/kg $MnCl_2$ by gavage for 40 d, Lee et al. (2006)

reported an increase in serum LH, FSH, and testosterone levels, sperm production, and efficiency of spermatogenesis. The mechanism of action underlying the release of Mn-mediated LHRH was analyzed in an in vitro study in which medial basal hypothalamus cells were treated with increasing concentrations (0, 50, 250, or 500 μM) of $MnCl_2$. The findings of this study lend support to the postulation that LHRH release is due to activation by Mn of the nitric oxide synthase (NOS)/nitric oxide (NO) system, which, in turn, augments production of cyclic guanosine monophosphate (cGMP), and activity of a cGMP-dependent protein kinase (PKG) produces the release of hormone from nerve terminations (Prestifilippo et al., 2007). Nevertheless, data obtained from a similar in vitro study failed to confirm direct activation of the nitric oxide synthase (NOS)/nitric oxide (NO) system by Mn suggesting that this metal acts by activating the soluble guanylyl cyclase (sGC) that subsequently triggers the cGMP-PKG system (Lee et al., 2007).

Finally, Mn does not seem to produce lipid peroxidation in human sperm (Huang et al., 2001). In fact, the incubation of human semen from 5 healthy volunteers with 0, 5, 50, or 500 ppm Mn nitrate showed no marked effect in mean sperm motility and did not markedly affect seminal MDA formation. At 500 ppm an inhibition of sperm motility was observed, but this effect is not biologically or environmentally relevant because of the high concentration of the metal.

Zinc

Zinc (Zn) is a chalcophilic element like Cu and Pb, and a trace constituent in most rocks. Zinc rarely occurs naturally in its metallic state, but many minerals contain Zn as a major component from which the metal may be economically recovered (WHO, 2001). Zinc is mainly used as a protective coating of other metals, such as iron and steel, but further important applications are in dye casting, the construction industry, and other alloys. This metal is a widely used catalyst and its inorganic compounds have various applications for automotive equipment, storage and dry-cell batteries, and organ pipes. Moreover, Zn chloride, sulfide, and sulfate have dental, medical, and household applications (WHO, 2001). With regard to Zn toxicity, high concentrations of metal in drinks (up to 2500 mg/L) have been linked with effects such as severe abdominal cramping, diarrhea, tenesmus, bloody stools, nausea, and vomiting (Brown et al., 1964), while the dermal application of Zn as Zn oxide has not been associated with any adverse dermal effects in humans (WHO, 2001). Occupational exposure to finely dispersed particulate matter formed when certain metals, including Zn, are volatilized may lead to an acute illness termed "metal-fume fever," characterized by a variety of symptoms including fever, chills, dyspnea, nausea, and fatigue (WHO, 2001).

Epidemiologic studies examined the correlation between sperm quality (volume, density, motility, survival) and hematic and sperm Zn concentration. Data showed that Zn enhanced male fertility by exerting a positive influence on spermatogenesis. In fact, Zn levels in the sperm liquid of oligospermic and azoospermic subjects are substantially lower than in fertile men (Fuse et al., 1999; Chia et al., 2000; Ali et al., 2005; Yuyan et al., 2007). In a Chinese study, 1179 eligible men (aged 20–59 yr) were examined for semen quality and serum Zn concentrations (Yuyan et al., 2007). Results demonstrated that the risk of asthenozoospermia increased significantly when serum Zn was lower than 870 µg/L. Fuse et al. (1999) measured Zn concentrations in seminal plasma from 98 infertile male patients and 8 fertile males. Sperm concentration/motility samples were divided into five groups: azoospermic (group A), oligoasthenozoospermic (group B), oligozoospermic (group C), asthenozoospermic (group D), and normal (group E). Zinc concentrations in seminal plasma from group A (87 ± 51 µg/ml) and group B (134 ± 52 µg/ml) samples were significantly lower than those from any other group. Similar results were obtained in a study conducted on 107 infertile male patients and 103 fertile males (Chia et al., 2000). In fact, the geometric means of the seminal plasma Zn concentrations were significantly lower in the infertile group (183.6 mg/L) compared with the fertile group (274.6 mg/L), while there were no significant differences in the geometric means of the blood Zn concentration between the two groups. Moreover, seminal plasma Zn concentration was significantly correlated with sperm density, motility, and viability. Finally, serum and seminal plasma Zn levels were low in oligospermic and azoospermic subjects when compared with the normospermic control group in a study that

measured metal levels in fertile and infertile population to determine the relationship between serum and seminal plasma Zn levels (Ali et al., 2005)

The protective role and positive effect of this metal on spermatogenesis are probably due to its membrane-stabilizing and antioxidant activity and its ability to maintain sperm viability by inhibiting DNAases (Aitken & Clarkson, 1987). In fact, Zn appears to be a potent scavenger of excessive superoxide anions produced by defective spermatozoa and/or leukocytes in human semen after ejaculation. Thus, it seems that seminal plasma, because of its high content of Zn, exerts protective, antioxidant-like activity sufficient to cope with the excessive amount of superoxide anions (Gavella & Lipovac, 1998).

DISCUSSION AND CONCLUSIONS

In the past 20 yr, EDCs have been the subject of numerous studies undertaken by different research groups. These studies enabled (1) identification of a number of xenobiotics that alter the normal functioning of the endocrine system and (2) elucidation of mechanisms of action responsible for these alterations and (3) reported on possible adverse health effects. Nonetheless, current knowledge of EDCs is still incomplete. In fact, studies examining EDC-induced effects in humans yielded inconsistent and inconclusive results, which are responsible for the overall data being classified as "weak." This classification is not meant to downplay the potential effects of EDCs but rather to highlight the need for more rigorous studies (WHO, 2002).

To our knowledge this review represents the first attempt to summarize current data regarding the role of metals as EDCs. Some heavy metals such as Cd, Hg, As, Pb, Mn, and Zn affected the endocrine system, producing alterations in physiological functions (Table 1). Some of these adverse health effects are common to different metals, while other effects are specific. In fact, the stimulation of progesterone synthesis is produced by exposure to both Cd (Powlin et al., 1997; Massanyi et al., 2000) and Hg (Mondal et al., 1997). The negative effect on spermatogenesis was observed in experiments using As (Sarkar et al., 2003; Pant et al., 2004), Hg (Chowdhury et al., 1989), or Pb (Sokol & Berman, 1991; Kempinas et al., 1994; Gennart et al. 1999; Wadi & Ahmad, 1999; Bonde et al., 2002; Kasperczyk et al., 2008), while both Mn (Lee et al., 2006) and Zn (Fuse et al., 1999; Chia et al., 2000; Ali et al., 2005; Yuyan et al., 2007) stimulated spermatogenesis. Furthermore, alterations regarding onset of puberty were correlated with exposure to Pb (Iavicoli et al., 2004, 2006) or manganese (Pine et al., 2005). A reduction in plasma levels of testosterone was found in laboratory animals treated with Hg (Vachhrajani & Chowdhury, 1990; Drevnick & Sandheinrich, 2003) or Pb (Ronis et al., 1996), and finally, both Cd (Lafuente et al., 2003) and Mn (Pine et al., 2005) altered gonadotropin secretion in the hypothalamus. If exposure to different metals resulted in the same effect, then it is possible that these xenobiotics exert their influence on the endocrine system through the same mechanism of action. However, it is also possible that they might produce the same effect through different mechanisms of action. For this reason, a fuller understanding of the mechanisms of action is needed in order to reach a better comprehension of the role that some metals play as EDCs. Unfortunately, at the present time, only a few of these mechanisms have been elucidated (Table 2). In the future, one of the most important endpoints may therefore be the study and identification of the mechanisms of action that are responsible for the role of these metals as EDCs.

Some results observed in several experimental studies indicate the possibility of hormesis. In fact, biphasic dose-response relationships following both Cd and As exposure were reported for progesterone synthesis (Paksy et al., 1997; Powlin et al., 1997; Piasek & Laskey, 1999; Jolibois et al., 1999a, 1999b; Massanyi et al., 2000; Kawai et al., 2002) and for GR-, MR-, PR-, AR-, RAR-, and TR-mediated transcription activity (Kaltreider et al., 2001; Bodwell et al., 2004, 2006; Davey et al., 2008), respectively. It would be of great interest for future studies to ascertain whether this particular phenomenon also occurs following exposure to other metals.

Another important issue is that in all the studies reviewed the effects on the endocrine system were produced by exposure to a single metal. However, both environmental and occupational exposure to EDCs is much more complex since humans are simultaneously exposed to different

TABLE 1. Effects of Metals on Endocrine System

Metals	Effects	References
Cadmium	Alterations of the secretory patterns of pituitary hormones	Lafuente et al., 2003
	Stimulation of progesterone synthesis (low doses)	Powlin et al., 1997; Massanyi et al., 2000
	Inhibition of progesterone synthesis (high doses)	Paksy et al., 1997; Piasek and Laskey, 1999; Jolibois et al., 1999a; 1999b; Kawai et al., 2002
	Estrogenic effect	Garcia-Morales et al., 1994
	Increase in early delivery	Nishijo et al., 2002
	Lower birth weight	Frery et al., 1993; Nishijo et al., 2002
	Early onset of puberty	Johnson et al., 2003
Mercury	Stimulation of progesterone synthesis	Mondal et al., 1997
	Reduction in plasma levels of testosterone and 17-beta-estradiol	Drevnick and Sandheinrich, 2003; Vachhrajani and Chowdhury, 1990; Ng and Liu, 1990
	Reduction in sperm motility and sperm count	Chowdhury et al., 1989
	Increase in plasma levels of T4, TSH, estrone, and estradiol	Barregård et al., 1994; Ellingsen et al., 2000; Agusa et al., 2007; Abdelouahab et al., 2008
Arsenic	Increase in GR-, MR-, PR-, AR-, RAR-, and TR-mediated transcription (low doses)	Bodwell et al., 2004; Bodwell et al., 2006; Davey et al., 2008
	Inhibition of GR-, MR-, PR-, AR-, RAR-, and TR-mediated transcription (high doses)	Kaltreider et al., 2001; Bodwell et al., 2004; Davey et al., 2008
	Inhibition of ER-mediated transcription	Davey et al., 2007
	Estrogenic effect	Jana et al., 2006
	Inhibition of spermatogenesis	Sarkar et al., 2003; Pant et al., 2004; Jana et al., 2006
Lead	Alterations of affinity of estrogen and luteinizing hormone receptors	Wide, 1980; Wiebe and Barr, 1988; Wiebe et al., 1988
	Action at multiple sites on the hypothalamus–pituitary–gonadal axis	Ronis et al., 1996; Srivastava et al., 2004
	Reduction in serum levels of IGF-1, LH, testosterone and estradiol	Ronis et al., 1996; Dearth et al., 2002; Srivastava et al., 2004;
	Alterations of onset of puberty	Iavicoli et al., 2004; 2006
	Morphological and functional alterations of sperm	Sokol and Berman, 1991; Kempinas et al., 1994; Wadi and Ahmad, 1999; Gennart et al. 1999; Bonde et al., 2002; Kasperczyk et al., 2008
	Inhibition of GH synthesis	Huseman et al., 1992; Ronis et al., 1996
Manganese	Increase in serum levels of LH, FSH and testosterone	Pine et al., 2005; Lee et al., 2006
	Stimulation of spermatogenesis	Lee et al., 2006
	Stimulation in the secretion of LH and LHRH	Prestifilippo et al., 2007; Lee et al., 2007
	Early onset of puberty	Pine et al., 2005
Zinc	Stimulation of spermatogenesis	Fuse et al., 1999; Chia et al., 2000; Ali et al., 2005; Yuyan et al., 2007

classes of xenobiotics including metals but also to organic compounds that may act as EDCs. Few published studies are available on combinations of different metals or other classes of xenobiotics that affect the endocrine system. For this reason, at present it is not known whether mixtures of different EDCs (the so-called "cocktail effect") may have addictive, synergistic, or antagonistic effects (Waring & Harris, 2005). EDCs with the same mode of action are generally assumed to behave additively, but there are few examples in which this hypothesis has been tested (Latini et al., 2003). Furthermore, a key issue regarding exposure to a mixture of EDCs is whether EDCs produce combination effects when they are present at levels that individually do not induce observable effects or even at levels similar to those found in the general environment. On the basis of theoretical considerations and little experimental evidence available, the possibility of combination effects cannot easily be ruled out or confirmed (Kortenkamp, 2008). To fill this gap, there is an need for epidemiological, in vitro and in vivo studies that adopt a more holistic approach, instead of focusing on a single chemical.

Most of the evidence from experimental studies identified effects of metals on the endocrine system at exposure levels in excess of those encountered in the different environmental matrices or workplaces. Consequently, uncertainty remains with regard to the nature of the dose-response

TABLE 2. Mechanisms of Action of Metals as Endocrine Disruptors

Metals	Mechanisms of action	References
Cadmium	Bond with estrogen receptors	Garcia-Morales et al., 1994;
	Inhibition of transcription of the LDL-R	Jolibois et al., 1999b;
	Inhibition of $P450_{scc}$	Kawai et al., 2002
Mercury	Induction of 3 beta-hydroxysteroid dehydrogenase	Mondal et al., 1997
	Inhibition of the type I iodothyronine deiodinase	Barregård et al., 1994
Arsenic	Stimulation or inhibition of nuclear transcription activity mediated by several hormone receptors	Kaltreider et al., 2001
	Bond with estrogen receptors	Jana et al., 2006
Lead	Reduction of the expression of the steroidogenic acute regulatory protein (StAR)	Srivastava et al., 2004
	Inhibition of LH secretion	Srivastava et al., 2004; Ronis et al., 1996
	Increased lipid peroxidation in seminal plasma	Kapserczyk et al., 2008
	Increased ROS production	Hsu et al., 1998
Manganese	Activation of the soluble guanylyl cyclase (sGC) and of cGMP-PKG system	Prestifilippo et al., 2007; Lee et al., 2007
Zinc	Membrane-stabilizing activity	Aitken and Clarkson, 1987
	Antioxidant activity	
	Inhibition of DNAase	

curve at low-level exposures. It therefore seems clear that future studies need to focus on this issue by studying the potential adverse effects on the endocrine system produced by low-level exposures to metals and their respective mechanisms of action.

Finally, at the present time, only a few metals such as Cd, Hg, As, Pb, Mn, and Zn have been evaluated for their endocrine-disrupting potential. However, in the general and occupational environment numerous other metals are present that have not been systematically assessed for their effects on the endocrine and reproductive systems. For this reason, another important endpoint for future research will be to assess, through epidemiological, in vitro and in vivo studies, the potential role of these latter metals as EDCs.

REFERENCES

Abdelouahab, N., Mergler, D., Takser, L., Vanier, C., St-Jean, M., Baldwin, M., Spear, P. A., and Chan, H. M. 2008. Gender differences in the effects of organochlorines, mercury, and lead on thyroid hormone levels in lakeside communities of Quebec (Canada). *Environ. Res.* 107:380–392.

Agusa, T., Kunito, T., Iwata, H., Monirith, I., Chamnan, C., Tana, T. S., Subramanian, A., and Tanabe, S. 2007. Mercury in hair and blood from residents of Phnom Penh (Cambodia) and possible effect on serum hormone levels. *Chemosphere* 68:590–596.

Aitken, R. J., and Clarkson, J. S. 1987. Cellular basis of defective sperm function and its association with genesis of reactive oxygen species by human spermatozoa. *J. Reprod. Fertil.* 81:459–469.

Ali, H., Baig, M., Rana, M. F., Ali, M., Qasim, R., and Khem, A. K. 2005. Relationship of serum and seminal plasma zinc levels and serum testosterone in oligospermic and azoospermic infertile men. *J. Coll. Physicians Surg. Pak.* 15:671–673.

Ames, B. N., and Gold, L. S. 2000. Paracelsus to parascience: The environmental cancer distraction. *Mutat. Res.* 447:3–13.

Ansar, A. S. 2000. The immune system as a potential target for environmental estrogens (endocrine disrupters): A new emerging field. *Toxicology* 150:191–206.

Aronson, K. J., Miller, A. B., Woolcott, C. G., Sterns, E. E., Macready, D. R., Lickley, L. A. Fish, E. B., Hiraki, G. Y., Holloway, C., Ross, T., Hann, W. M., SenGupta, S. K., and Weber, J. P. 2000. Breast adipose tissue concentrations of polychlorinated biphenyls and other organochlorines and breast cancer risk. *Cancer Epidemiol. Biomarmarkers Prev.* 9:55–63.

Band, P. R., Le, N. D., Fang, R., and Deschamps, M. 2002. Carcinogenic and endocrine disrupting effects of cigarette smoke and risk of breast cancer. *Lancet* 360:1044–1049.

Barregård, L., Lindstedt, G., Schütz, A., and Sällsten, G. 1994. Endocrine function in mercury exposed chloralkali workers. *Occup. Environ. Med.* 51:536–540.

Bayen, S., Koroleva, E., Lee, H. K. and Obbard, J. P. 2005. Persistent organic pollutants and heavy metals in typical seafoods consumed in Singapore. *J. Toxicol. Environ. Health A* 68:151–166.

Berlin, M., Hua, J., Lödgberg, B., and Warfvinge, K. 1992. Prenatal exposure to mercury vapour: Effects on brain development. *Fundam. Appl. Toxicol.* 19:324–326.

Bernstam, L. and Nriagu, J. 2000. Molecular aspects of arsenic stress. *J. Toxicol. Environ. Health B* 3:293–322.

Bhan, A., and Sarkar, N. N. 2005. Mercury in the environment: Effect on health and reproduction. *Rev. Environ. Health* 20:39–56.

Bhattacharyya, M. H., Wilson, A. K., Rajan, S. S., and Jonah, M. 2000. Biochemical pathways in cadmium toxicity. In *Molecular biology and toxicology of metals*, eds. R. K. Zalup and J. Koropatnick, pp. 34–74. London: Taylor & Francis.

Bodwell, J. E., Gosse, J. A., Nomikos, A. P., and Hamilton, J. W. 2006. Arsenic disruption of steroid receptor gene activation: Complex dose-response effects are shared by several steroid receptors. *Chem. Res. Toxicol.* 19:1619–1629.

Bodwell, J. E., Kingsley, L. A., and Hamilton, J. W. 2004. Arsenic at very low concentrations alters glucocorticoid receptor (GR)-mediated gene activation but not GR-mediated gene repression: Complex dose-response effects are closely correlated with levels of activated GR and require a functional GR DNA binding domain. *Chem. Res. Toxicol.* 17:1064–1076.

Bonde, J. P., Joffe, M., Apostoli, P., Dale, A., Kiss, P., Spano, M., Caruso, F., Giwercman, A., Bisanti, L., Porru, S., Vanhoorne, M., Comhaire, F., and Zschiesche, W. 2002. Sperm count and chromatin structure in men exposed to inorganic lead: Lowest adverse effect levels. *Occup. Environ. Med.* 59:234–242.

Brown, M. A., Thom, J. V., Otth, G. L., Cova, P., and Juarez, J. 1964. Food poisoning involving zinc contamination. *Arch. Environ. Health* 8:657–660.

Calne, D. B., Chu, N. S., Huang, H. H., Lu, C. S., and Olanow, W. 1994. Manganism and idiopathic parkinsonism: Similarities and differences. *Neurology* 44:1583–1586.

Chia, S. E., Ong, C. N., Chua, L. H., Ho, L. M., and Tay, S. K. 2000. Comparison of zinc concentrations in blood and seminal plasma and the various sperm parameters between fertile and infertile men. *J. Androl.* 21:53–57.

Choi, S. M., Yoo, S. D., and Lee, B. M. 2004. Toxicological characteristics of endocrine-disrupting chemicals: Developmental toxicity, carcinogenicity and mutagenicity. *J. Toxicol. Environ. Health B* 7:1–24.

Chowdhury, A. R., Makhija, S., Vachhrajani, K. D., and Gautam, A. K. 1989. Methylmercury- and mercuric-chloride-induced alterations in rat epididymal sperm. *Toxicol. Lett.* 47:125–134.

Colborn, T., Dumanoski, D., and Myers, J. P. 1996. *Our stolen future: Are we threatening our fertility, intelligence and survival?* New York: Penguin Group.

Couper, J. 1837. On the effects of black oxide of manganese when inhaled into the lungs. *Br. Ann. Med. Pharm.* 1:41–42.

Counter, A. S., Buchanan, L. H., and Ortega, F. 2009. Neurophysiologic and neurocognitive case profiles of Andean patients with chronic environmental poisoning. *J. Toxicol. Environ. Health A* 72:625–632.

Davey, J. C., Bodwell, J. E., Gosse, J. A., and Hamilton, J. W. 2007. Arsenic as an endocrine disruptor: Effects of arsenic on estrogen receptor-mediated gene expression in vivo and in cell culture. *Toxicol. Sci.* 98:75–86.

Davey, J. C., Nomikos, A. P., Wungjiranirun, M., Sherman, J. R., Ingram, L., Batki, C., Lariviere, J. P., and Hamilton, J. W. 2008. Arsenic as an endocrine disruptor: Arsenic disrupts retinoic acid receptor- and thyroid hormone receptor-mediated gene regulation and thyroid hormone-mediated amphibian tail metamorphosis. *Environ. Health Perspect.* 116:165–172.

Davis, B. J., Price, H. C., O'Connor, R. W., Fernando, R., Rowland, A. S., and Morgan, D. L. 2001. Mercury vapor and female reproductive toxicity. *Toxicol. Sci.* 59:291–296.

Dearth, R. K., Hiney, J. K., Srivastava, V., Burdick, S. B., Bratton, G. R., and Dees, W. L. 2002. Effects of lead (Pb) exposure during gestation and lactation on female pubertal development in the rat. *Reprod. Toxicol.* 16:343–352.

De Rosa, C., Richter, P., Pohl, H., and Jones, D. E. 1998. Environmental exposures that affect the endocrine system: Public health implications. *J. Toxicol. Environ. Health B* 1:3–26.

Drevnick, P. E., and Sandheinrich, M. B. 2003. Effects of dietary methylmercury on reproductive endocrinology of fathead minnows. *Environ. Sci. Technol.* 37:4390–4396.

Ellingsen, D. G., Efskind, J., Haug, E., Thomassen, Y., Martinsen, I., and Gaarder, P. I. 2000. Effects of low mercury vapour exposure on the thyroid function in chloralkali workers. *J. Appl. Toxicol.* 20:483–489.

Frery, N., Nessmann, C., Girard, F., Lafond, J., Moreau, T., Blot, P., Lellouch, J., and Huel, G. 1993. Environmental exposure to cadmium and human birth weight. *Toxicology* 79:109–118.

Fuse, H., Kazama, T., Ohta, S., and Fujiuchi, Y. 1999. Relationship between zinc concentrations in seminal plasma and various sperm parameters. *Int. Urol. Nephrol.* 31:401–408.

Garcia-Morales, P., Saceda, M., Kenney, N., Salomon, D. S., Kim, N., Salomon, D. S., Gottardis, M. M., Solomon, H. B., Sholler, P. F., Jordan, V. C., and Martin, M. B. 1994. Effect of cadmium on estrogen receptor levels and estrogen-induced responses in human breast cancer cells. *J. Biol. Chem.* 269:16896–16901.

Gavella, M., and Lipovac, V. 1998. In vitro effect of zinc on oxidative changes in human semen. *Andrologia* 30:317–323.

Gennart, J. P., Buchet, J. P., Roels, H., Ghyselen, P., Ceulemans, E., and Lauwerys, R. 1992. Fertility of male workers exposed to cadmium, lead, or manganese. *Am. J. Epidemiol.* 135:1208–1219.

Gochfeld, M. 2003. Cases of mercury exposure, bioavailability, and absorption. *Ecotoxicol. Environ. Safety* 56:174–179.

Golub, M. S., Macintosh, M. S., and Baumrind, N. 1998. Developmental and reproductive toxicity of inorganic arsenic: Animal studies and human concerns. *J. Toxicol. Environ. Health B* 1:199–241.

Hsu, P., Hsu, C., Liu, M., Chen, L., and Guo Y. L. 1998. Lead-induced changes in spermatozoa function and metabolism. *J. Toxicol. Environ. Health A* 55:45–64.

Huang, B., Lai, H., and Liu, M. 2002. Concentration dependency in lead-inhibited steroidogenesis in MA-10 mouse Leydig tumor cells. *J. Toxicol. Environ. Health A* 65:557–567.

Huang, Y., Tseng, W., and Lin T. 2001. In vitro effects of metal ions (Fe^{2+}, Mg^{2+}, Pb^{2+}) on sperm motility and lipid peroxidation in human semen. *J. Toxicol. Environ. Health A* 62:259–267.

Huseman, C. A., Varma, M. M., and Angle, C. R. 1992. Neuroendocrine effects of toxic and low blood lead levels in children. *Pediatrics* 90:186–189.

Iavicoli, I., Carelli, G., Stanek, E. J., Castellino, N., and Calabrese, E. J. 2004. Effects of low doses of dietary lead on puberty onset in female mice. *Reprod. Toxicol.* 19:35–41.

Iavicoli, I., Carelli, G., Stanek, E. J, Castellino, N., Li, Z., and Calabrese, E. J. 2006. Low doses of dietary lead are associated with a profound reduction in the time to the onset of puberty in female mice. *Reprod. Toxicol.* 4:586–590.

International Agency for Research on Cancer (IARC). 1993. Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. *IARC Monogr. Eval. Carcinogen. Risks Hum.* 58.

International Agency for Research on Cancer (IARC). 1998. Some metals and metallic compounds. *IARC Monogr. Eval. Carcinogen. Risks Hum.* 23.

Jana, K., Jana, S., and Samanta, P. K. 2006. Effects of chronic exposure to sodium arsenite on hypothalamo-pituitary-testicular activities in adult rats: Possible an estrogenic mode of action. *Reprod. Biol. Endocrinol.* 16:4–9.

Jarup, L., Berglund, M., Elinder, C. G., Nordberg, G., and Vahter, M. 1998. Health effects of cadmium exposure—A review of the literature and risk estimate. Scand. *J. Work Environ. Health* 24(Suppl. 1):1–52.

Johnson, M. D., Kenney, N., Stoica, A., Hillakivi-Clarke, L., Singh, B., Chepko, G., Clarke, R., Sholler, P. F., Lirio, A. A., Foss, C., Reiter, R., Trock, B., Paik, S., and Martin, M. B. 2003. Cadmium mimics the in vivo effects of estrogen in the uterus and mammary gland. *Nat. Med.* 9:1081–1084.

Jolibois, L. S., Jr., Burow, M. E., Swan, K. F., George, W. J., Anderson, M. B., and Henson, M. C. 1999a. Effects of cadmium on cell viability, trophoblastic development, and expression of low density lipoprotein receptor transcripts in cultured human placental cells. *Reprod. Toxicol.* 13:473–480.

Jolibois, L. S. Jr., Shi, W., George, W. J,, Henson, M. C., and Anderson, M. B. 1999b. Cadmium accumulation and effects on progesterone release by cultured human trophoblast cells. *Reprod. Toxicol.* 13:215–221.

Junaid, M., Chowdhuri, D. K., Narayan, R., Shanker, R., and Saxena, D. K. 1997. Lead-induced changes in ovarian follicular development and maturation in mice. *J. Toxicol. Environ. Health A* 50:31–40.

Kaltreider, R. C., Davis, A. M., Lariviere, J. P., and Hamilton, J. W. 2001. Arsenic alters the function of the glucocorticoid receptor as a transcription factor. *Environ. Health Perspect.* 109:245–251.

Kasperczyk, A., Kasperczyk, S., Horak, S., Ostalowska, A., Grucka-Mamczar, E., Romuk, E., Olejek, A., and Birkner, E. 2008. Assessment of semen function and lipid peroxidation among lead exposed men. *Toxicol. Appl. Pharmacol.* 228:378–384.

Katawa, M. 2008. Sex, stress, and neuron: Molecular mechanism of peptides and steroids with their receptors on the nervous system. *Curr. Opin. Pharmacol.* 8:729–730.

Kawai, M., Swan, K. F., Green, A. E., Edwards, D. E., Anderson, M. B., and Henson, M. C. 2002. Placental endocrine disruption induced by cadmium: Effects on P450 cholesterol side-chain cleavage and 3b-hydroxysteroid dehydrogenase enzymes in cultured human trophoblasts. *Biol. Reprod.* 67:178–183.

Keller-Byrne, J. E., Khuder, S. A., and Schaub, E. A. 1997. Meta-analyses of prostate cancer and farming. *Am. J. Ind. Med.* 31:580–586.

Kempinas, W. G., Farvaretto, A. L. V., Melo, V. R., Lamano, C., Petenusci, S. O., and Oliveira-Filho, R. M. 1994. Time-dependent effects of lead on rat reproductive functions. *J. Appl. Toxicol.* 14:427–433.

Kortenkamp, A. 2008. Low dose mixture effects of endocrine disrupters: Implications for risk assessment and epidemiology. *Int. J. Androl.* 31:233–240.

Kotsonis, F. N., and Klaassen, C. D. 1977. Toxicity and distribution of cadmium administered to rats at sublethal doses. *Toxicol. Appl. Pharmacol.* 41:667–680.

Kunz, P. Y., and Fent, K. 2006. Estrogenic activity of UV filter mixtures. *Toxicol. Appl. Pharmacol.* 217:86–99.

Lafuente, A., Cano, P., and Esquifino, A. I. 2003. Are cadmium effects on plasma gonadotropins, prolactin, ACTH, GH and TSH levels, dose-dependent? *Biometals* 16:243–250.

Latini, G., De Felice, C., Presta, G., Del Vecchio, A., Paris, I., Ruggieri, F., and Mazzeo, P. 2003. Exposure to DEHP in humans during pregnancy. A preliminary report. *Biol. Neonate* 83:22–24.

Lee, B., Hiney, J. K., Pine, M. D., Srivastava, V. K., and Dees, W. L. 2007. Manganese stimulates luteinizing hormone releasing hormone secretion in prepubertal female rats: Hypothalamic site and mechanism of action. *J. Physiol.* 578:765–772.

Lee, B., Pine, M., Johnson, L., Rettori, V., Hiney, J. K., and Dees, W. L. 2006. Manganese acts centrally to activate reproductive hormone secretion and pubertal development in male rats. *Reprod Toxicol.* 22:580–585.

Leoni, G., Bogliolo, L., Deiana, G., Berlinguer, F., Rosati, I., Pintus, P. P., Ledda, S., and Naitana, S. 2002. Influence of cadmium exposure on in vitro ovine gamete dysfunction. *Reprod. Toxicol.* 16:371–377.

Liu, J., Xie, Y., Cooper, R., Ducharme, D. M., Tennant, R., Diwan, B. A., and Waalkes, M. P. 2007. Transplacental exposure to inorganic arsenic at a hepatocarcinogenic dose induces fetal gene expression changes in mice indicative of aberrant estrogen signalling and disrupted steroid metabolism. *Toxicol. Appl. Pharmacol.* 220:284–291.

Mantovani, A. 2002. Hazard identification and risk assessment of endocrine disrupting chemicals with regard to developmental effects. *Toxicology* 181:367–370.

Mantovani, A., Stazi, A. V., Macri, C., Maranghi, F., and Ricciardi, C. 1999. Problems in testing and risk assessment of endocrine disrupting chemicals with regard to developmental toxicology. *Chemosphere* 39:1293–1300.

Massanyi, P, Uhrin, V, Sirotkin, A V, Paksy, K, Forgács, Z. S., Toman, R., and Kovacik, J. 2000. Effects of cadmium on ultrastructure and steroidogenesis in cultured porcine ovarian granulosa cells. *Acta Vet. Brno* 69:101–106.

Mondal, S., Mukhopadhyay, B., and Bhattacharya, S., 1997. Inorganic mercury binding to fish oocyte plasma membrane induces steroidogenesis and translatable messenger RNA synthesis. *Biometals* 10:285–290.

National Toxicology Program. 2001. *Endocrine disrupters low dose peer review*. Research Triangle Park, NC. National Institute of Environmental Health Sciences.

Ng, T. B., and Liu, W. K. 1990. Toxic effect of heavy metals on cells isolated from the rat adrenal and testis. *In Vitro Cell Dev. Biol.* 26:24–28.

Nishijo, M., Nakagawa, H., Honda, R., Tanebe, K., Saito, S., Teranishi, H., and Tawara, K. 2002. Effects of maternal exposure to cadmium on pregnancy outcome and breast milk. *Occup. Environ. Med.* 59:394–397.

Oishi, S. 2002. Effects of propyl paraben on the male reproductive system. *Food Chem. Toxicol.* 40:1807–1813.

Olanow, C. W. 2004. Manganese-induced parkinsonism and Parkinson's disease. *Ann. NY Acad. Sci.* 1012:209–223.
Ozawa, H. 2005. Steroid hormones, their receptors and neuroendocrine system. *J. Nippon Med. School* 72:316–325.
Paksy, K., Gati, I., Naray, M., and Rajczy K. 2001. Lead accumulation in humanovarian follicular fluid and in vitro effect of lead on progesterone production by cultured human ovarian granulosa cells. *J. Toxicol. Environ. Health A* 62:359–366.
Paksy, K., Rajczy, K., Forgács, Z., Lázár, P., Bernard, A., Gáti, I., and Kaáli, G. S. 1997. Effect of cadmium on morphology and steroidogenesis of cultured human ovarian granulosa cells. *J. Appl. Toxicol.* 17:321–327.
Pant, N., Murty, R. C., and Srivastava, S. P. 2004. Male reproductive toxicity of sodium arsenite in mice. *Hum. Exp. Toxicol.* 23:399–403.
Piasek, M., and Laskey, J. W. 1994. Acute cadmium exposure and ovarian steroidogenesis in cycling and pregnant rats. *Reprod. Toxicol.* 8:495–507.
Piasek, M., and Laskey, J. W. 1999. Effects of in vitro cadmium exposure on ovarian steroidogenesis in rats. *J. Appl. Toxicol.* 19:211–217.
Pine, M., Lee, B., Dearth, R., Hiney, J. K., and Dees, W. L. 2005. Manganese acts centrally to stimulate luteinizing hormone secretion: A potential influence on female pubertal development. *Toxicol. Sci.* 85:880–885.
Powlin, S. S., Keng, P. C., and Miller, R. K. 1997. Toxicity of cadmium in human trophoblast cells (JAr choriocarcinoma): Role of calmodulin and the calmodulin inhibitor, zaldaride maleate. *Toxicol. Appl. Pharmacol.* 144:225–234.
Prestifilippo, J. P., Fernández-Solari, J., Mohn, C., De Laurentiis, A., McCann, S. M., Dees, W., and Rettori, V. 2007. Effect of manganese on luteinizing hormone-releasing hormone secretion in adult male rats. *Toxicol. Sci.* 97:75–80.
Ratcliffe, H. E., Swanson, G. M., and Fischer, L. J. 1996. Human exposure to mercury: A critical assessment of the evidence of adverse health effects. *J. Toxicol. Environ. Health* 49:221–270.
Ratnaike, R. N. 2003. Acute and chronic arsenic toxicity. *Postgrad Med J.* 79:391–396.
Rodier, P. M. 2004. Environmental causes of central nervous system mal-development. *Pediatrics* 113:1076–1083.
Ronis, M. J., Badger, T. M., Shema, S. J., Roberson, P. K., and Shaikh, F. 1996. Reproductive toxicity and growth effects in rats exposed to lead at different periods during development. *Toxicol. Appl. Pharmacol.* 136:361–371.
Ronis, M. J. J., Badger, T. M., Shema, S. J., Roberson, P. K., and Shaikh, F. 1998a. Effects on pubertal growth and reproduction in rats exposed to lead perinatally or continuously throughout development. *J. Toxicol. Environ. Health A* 53:327–341.
Ronis, M. J. J., Gandy, J., and Badger, T. 1998b. Endocrine mechanisms underlying reproductive toxicity in the developing rat chronically exposed to dietary lead. *J. Toxicol. Environ. Health A.* 54:77–99.
Roy, D., Palangat, M., Chen, C.-W., Thomas, R. D., Colerangle, J., Atkinson, A., and Yan, Z.-J. 1997. Biochemical and molecular changes at the cellular level in response to exposure to environmental estrogen-like chemicals. *J. Toxicol. Environ. Health* 50:1–29.
Safe, S. H. 2000. Endocrine disruptors and human health—Is there a problem? An update. *Environ. Health Perspect.* 108:487–493.
Santamaria, A. B. 2008. Manganese exposure, essentiality and toxicity. *Indian J. Med. Res.* 128:484–500.
Santamaria, A. B., Cushing, C. A., Antonini, J. M., Finley, B. L., and Mowat, F. S. 2007. State-of-the-science review: Does manganese exposure during welding pose a neurological risk? *J. Toxicol. Environ. Health B* 10:417–465.
Saric, M. 1986. *Handbook on the toxicology of metals*, Vol. II: *Specific metals*, pp. 354–386. New York: Elsevier Science.
Sarkar, M., Ray Chaudhuri, G., Chattopadhyay, A., and Biswas, N. M. 2003. Effect of sodium arsenite on spermatogenesis, plasma gonadotrophins and testosterone in rats. *Asian J. Androl.* 1:27–31.
Satoh, M., Koyama, H., Kaji, T., Kito, H., and Tohyama, C. 2002. Perspectives on cadmium research. *Tohoku J. Exp. Med.* 196:23–32.
Schuurs, A. H. 1999. Reproductive toxicity of occupational mercury. A review of the literature. *J. Dent.* 27:249–256.
Smida, A. D., Valderrama, X. P., Agostini, M. C., Furlan, M. A., and Chedrese, J. 2004. Cadmium stimulates transcription of the cytochrome p450 side chain cleavage gene in genetically modified stable porcine granulosa cells. *Biol. Reprod.* 70:25–31.
Sokol, R. Z., and Berman, N. 1991. The effect of age of exposure on lead-induced testicular toxicity. *Toxicology* 69:269–278.
Srivastava, V., Dearth, R. K., Hiney, J. K., Ramirez, L. M., Bratton, G. R., and Dees, W. L. 2004. The effects of low-level Pb on steroidogenic acute regulatory protein (StAR) in the prepubertal rat ovary. *Toxicol. Sci.* 77:35–40.
Stoica, A., Pentecost, E., and Martin, M. B. 2000 Effects of arsenite on estrogen receptor-alpha expression and activity in MCF-7 breast cancer cells. *Endocrinology.* 141:3595–602.
Surkan, P. J., Zhang, A., Trachtenberg, F., Daniel, D. B., McKinlay, S., and Bellinger, D. C. 2007. Neuropsychological function in children with blood lead levels <10 microg/dl. *Neurotoxicology* 28:1170–1177.
Sweet, L. I., and Zelikoff, J. T. 2001. Toxicology and immunotoxicology of mercury: A comparative review in fish and humans. *J. Toxicol. Environ. Health B* 4:161–205.
Tam, P. P. L., and Liu, W. K. 1985 Gonadal development and fertility of mice treated prenatally with cadmium during the early organogenesis stages. *Teratology* 32:453–462.
Téllez-Rojo, M. M., Bellinger, D. C., Arroyo-Quiroz, C., Lamadrid-Figueroa, H., Mercado-García, A., Schnaas-Arrieta, L., Wright, R. O., Hernández-Avila, M., and Hu, H. 2006. Longitudinal associations between blood lead concentrations lower than 10 microg/dl and neurobehavioral development in environmentally exposed children in Mexico City. *Pediatrics* 118:e323–e330.
Tilson, H. A. 1998. Developmental neurotoxicology of endocrine disruptors and pesticides: Identification of information gaps and research needs. *Environ. Health Perspect.* 106:807–811.
Tsai, S.-M., Wang, T.-N., and Ko, Y.-C. 1998. Cancer mortality trends in a blackfoot disease endemic community of Taiwan following water source replacement. *J. Toxiciol. Environ. Health A* 55: 389–404.
Tseng, C. H., Chong, C. K., Tseng, C. P., Hsueh, Y. M., Chiou, H. Y., Tseng, C. C., and Chen C. J. 2003. Long-term arsenic exposure and ischemic heart disease in arseniasis-hyperendemic villages in Taiwan. *Toxicol. Lett.* 137:15–21.
Vachhrajani, K. D., and Chowdhury, A. R. 1990. Distribution of mercury and evaluation of testicular steroidogenesis in mercuric chloride and methylmercury administered rats. *Indian J. Exp. Biol.* 28:746–751.
Vahidnia, A., van der Voet, G. B., and de Wolff, F. A. 2007. Arsenic neurotoxicity—A review. *Hum. Exp. Toxicol.* 26:823–832.
Wadi, S. A., and Ahmad, G. 1999. Effects of lead on the male reproductive system in mice. *J. Toxicol. Environ. Health A* 56:513–521.

Waring, R. H., and Harris, R. M. 2005. Endocrine disrupters: A human risk? *Mol. Cell. Endocrinol.* 244:2–9.

Watson, W. H., and Yager, J. D. 2007. Arsenic: Extension of its endocrine disruption potential to interference with estrogen eeceptor-mediated signaling. *Toxicol. Sci.* 98:1–4.

Weir, H. K., Marrett, L. D., Kreiger, N., Darlington, G. A., and Sugar, L. 2000. Pre-natal and peri-natal exposures and risk of testicular germ-cell cancer. *Int. J. Cancer* 87:438–443.

Weisglas-Kuperus, N., Vreugdenhil, H. J., and Mulder, P. G. 2004. Immunological effects of environmental exposure to PCBs and dioxins in Dutch children. *Toxicol. Lett.* 149:281–285.

Wennborg, H., Bonde, J. P., Stenbeck, M., and Olsen, J. 2002. Adverse reproduction outcomes among employees working in biomedical research laboratories. *Scand. J. Work Environ. Health* 28:5–11.

Wide, M. 1980. Interference of lead with implantation in the mouse: effect of exogenous oestradiol and progesterone. *Teratology* 21:187–191.

Wiebe, J. P., and Barr, K. J. 1988. Effect of prenatal and neonatal exposure to lead on the affinity and number of estradiol receptors in the uterus. *J. Toxicol Environ Health* 24:451–460.

Wiebe, J. P., Barr, K. J., and Buckingham, K. D. 1988. Effect of prenatal and neonatal exposure to lead on gonadotropin receptors and steroidogenesis in rat ovaries. *J. Toxicol. Environ. Health* 24:461–476.

Wier, P. J., Miller, R. K., Maulik, D., and DiSant'Agnese, P. A. 1990. Toxicity of cadmium in the perfused human placenta. *Toxicol. Appl. Pharmacol.* 105:156–171.

World Health Organization. 1995. *Inorganic lead. Environmental health criteria 165*. Geneva: International Programme on Chemical Safety.

World Health Organization. 2001. *Zinc. Environmental health criteria 221*. Geneva: International Programme on Chemical Safety.

World Health Organization. 2002. *Global assessment of the state-of-the-science of endocrine disruptors*, eds. T. Damstra, S. Barlow, A, Bergman, R. Kavlock, and V. Der Kraak. Geneva: WHO.

Wormley, D. D., Ramesh, A., and Hood, D. B., 2004. Environmental contaminant-mixture effects on CNS development, plasticity and behaviour. *Toxicol. Appl. Pharmacol.* 197:49–65.

Yuyan, L., Junqing, W., Wei, Y., Weijin, Z., and Ersheng, G. 2008. Are serum zinc and copper levels related to semen quality? *Fertil. Steril.* 89:1008–1011.

Zadorozhnaja, T. D., Little, R. E., Miller, R. K., Mendel, N. A., Taylor, R. J., Presley, B. J., and Gladen, B. C. 2000.Concentrations of arsenic, cadmium, copper, lead, mercury, and zinc in human placentas from two cities in Ukraine. *J. Toxicol. Environ. Health* 61:255–263.